THE INFLUENCE OF SOME PRE-AND PEROPERATIVE FACTORS ON POSTOPERATIVE MORTALITY AND RENAL FUNCTION IN OPEN-HEART SURGERY

A Clinical Study with the Aid of Multiple Regression Analysis and Computer Treatment of Data

by

Stig Nordlund

Uppsala 1966

With the statistical collaboration of Gunnar Eklund

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CONTENTS

	INTRODUCTION	3
Chapter I	REVIEW OF LITERATURE	5
	A. Perfusion systems, prime with blood and hemodilution	5
	B. Use of low-molecular-weight dextran in open-heart surgery	7
	C. Acute renal failure and open-heart surgery	7
	D. Use of mannitol in open-heart surgery	9
	E. Mortality after open-heart surgery	9
	F. Use of computers in medicine	10
Chapter II	MATERIAL AND CLINICAL TREATMENT	11
	A. Clinical material and principles of selection	11
	B. Clinical treatment	12
	C. Changes in technique during the investigation period	14
	D. Summary of patient material	15
Chapter III	REGISTRATION AND STATISTICAL TREATMENT OF DATA	17
	A. Recording data for computer treatment	17
	B. Statistical methods	23
Chapter IV	INFLUENCE OF PREOPERATIVE STATE ON MORTALITY WITHIN 30 DAYS AFTER OPERATION	29
	A. The material and the variables studied	29
	B. Simple correlation analysis between mortality and preoperative variables	30
	C. Multiple-regression analysis	30
	D. Application of multiple regression analysis to the material	31
	1.(a) Changes of coefficient values within the same analysis	32
	(b) Influence of different levels of probability	32
	(c) Influence of differences in composition of the material	32
	(d) Influence of re-insertion of deleted variables	32
	(e) Absurd predicted values and influence of differentiated individual weightings	33
	(f) Results of preliminary investigations: Summary	33
	2. Program for final analysis	34
	3. Interpretation of coefficients	35
	4. Prediction of death risk	40
	5. Forecast index	43
	E. Discussion	47
Chapter V	INFLUENCE OF PRE- AND PEROPERATIVE FACTORS ON 30-DAY POSTOPERATIVE MORTALITY	53
Chapter VI	RENAL FUNCTION AFTER EXTRACORPOREAL CIRCULATION	59
	Introduction	59
	A. Steps in analysis	59
	B. Results	60

1. The classification in three groups with different postoperative renal functions 60
2. The effect of both pre- and peroperative factors on postoperative renal function 62
(a) General factors 62
(b) Comparison between the bubble and the disc oxygenators 67
(c) Influence of the addition of Rheomacrodex® and/or mannitol to the priming volume 68
C. Discussion 70

Chapter VII GENERAL DISCUSSION AND SUMMARY OF ESSENTIAL FINDINGS 75
CONCLUSIONS 83

Appendix I Figures and Tables 87

Appendix II Abbreviations and Units 121

Appendix III References 125

INTRODUCTION

Open-heart surgery is developing so rapidly that it is difficult to collect series of similar cases without great changes in operation or perfusion technique or postoperative care being introduced meanwhile. Comparisons between materials from different clinics are also difficult to evaluate, owing to the difference in the methods of selecting patients and in the techniques employed.

With the emergence of the modern technique of data-processing it has become possible to carry out prognosis analyses, taking a very large number of factors into account. However, such an analysis is complicated by the fact that a very large number of data (variables) are recorded for each patient, both pre-, per- and postoperatively. Using such technique, some of the problems in open-heart surgery are discussed in this paper.

The shortage of blood, especially freshly drawn heparinized blood, has led, on the one hand, to attempts being made to reduce the priming volume in the oxygenators of heart-lung machines and, on the other, to blood being replaced by other fluids, for example, low-molecular-weight dextran.

Open-heart surgery with extra-corporeal circulation (ECC) is reported to be one of the most common causes of postoperative tubular necrosis. In order to reduce the risk of such a complication, the addition of mannitol to the priming volume or the patient´s blood has been recommended. The effect of this is disputed.

The oxygenators most often used at present are of either the bubble or the disc type. Comparisons between these two systems have not been made simultaneously on clinical material from the same clinic.

Against the background of these facts, the purpose of the present investigation was as follows:

(1) To study if multiple statistical regression analysis and data-processing technique was suitable to calculate the prognostic significance of certain (a) preoperative and (b) both pre- and peroperative factors for mortality within 30 days and for the postoperative renal function in a clinical material of patients who had been treated by routine methods. In this way it should be possible to obtain, on the bases of preoperative data, an estimate of the probability of the patient´s surviving and thus to predict the mortality risk of the operation.

(2) To evaluate by the same analytical method the effect on the postoperative renal function of the addition of mannitol and/or low-molecular weight dextran to the priming volume. Since these additions were not made purely by chance, the patient´s preoperative status must be taken into account in the analysis.

(3) To compare the postoperative renal functions of patients who had been operated upon with the aid of a disc oxygenator or a bubble oxygenator. Here also each patient´s preoperative status must be taken into account, as the bubble oxygenator was only used alongside the disc oxygenator during the last year of the investigation and as the possibility cannot be precluded that the selection of patients may have been altered during that time.

(4) To construct, on the basis of preoperative data, a forecast index that could be used for the prediction of operative risk, and to test this index on other patients than those included in the analysis.

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CHAPTER I

REVIEW OF LITERATURE

A. PERFUSION SYSTEMS, PRIME WITH BLOOD AND HEMODILUTION

Despite its often complex construction, the actual function of the heart-lung machine is a simple one, namely, to provide the tissues of the body with a sufficient quantity of oxygen and to remove carbon dioxide.

Two types of systems have so far been successful, namely, film oxygenators and bubble oxygenators. Historical backgrounds and data on the functioning and performance of these systems will be found in Björk (1948) and De Wall, Grage, McFee & Chiechi (1961).

Clinical application of perfusion systems based on the bubble principle has been made possible thanks to the success which has been achieved in utilizing antifoamers (Clark, Gollan & Gupta 1950). The design of the bubble oxygenator utilized in part of the present study was first described by Rügg & Kyvsgaard (1957).

Priming with blood

Though it is difficult to demonstrate that better clinical results can be obtained with hemodilution than when blood alone is used, the method possesses considerable practical advantages.

Most of the perfusion systems currently in use still need a considerable amount of blood, averaging about 4 l, for priming (Sgouris, Mc Call, Coryell, Gallick, Hyndman & Andersen 1962). The practical disadvantages of this requirement are obvious, as it involves heavy demands on the blood banks (Britten, Salzman, Grove-Rasmussen & Shaw 1963). Thus Krumhaar, Foote & Maloney (1963) state that an average of 19.9 bottles of blood were requisitioned for every open-heart operation that was planned in the Los Angeles area. If only freshly obtained not more than 24 hours old heparinized blood may be used, operations must be planned a long time in advance and no last-minute changes or treatment of acute cases are possible. The authors therefore recommend the use of converted ACD stored blood instead of heparinized. They report that the red blood cell survival time is the same for 24 hours old heparinized and ACD-blood. The greater the amount of homologous blood used, the greater is the risk of incompatibility. At present, the only test made is to ascertain whether the red corpuscles agglutinate in foreign serum, the adaptability of the other constituents of the blood being disregarded. Research into these aspects is currently in progress (for example Schrek & Neville (1964) who found that neutrophils in mixed blood have a shortened life span). This state of affairs has led Gadboys, Slonim & Litwak (1962; see also Litwak, Gilson, Slonim, McCune, Kiem & Gadboys 1961) to introduce the concept of "the homologous blood syndrome". These authors maintain that incompatibility exists between thrombocytes, white corpuscles and plasma-protein fractions, both between the patient and the donors, and between different individual donors. Therefore, when homologous blood is circulated extracorporeally, hypotension, thrombocytopenia, leucopenia, and sequestering of blood occur during perfusion, as well in addition a tendency to pulmonary edema and kidney and brain damage developes afterwards, when the sequestered blood is returned into the circulation. In a material of 36 patients, these authors found sequestration of blood amounting on the average to 15.4 ml/kg, and four out

of seven deaths were believed to have been caused by "hypovolemia". Similar results are reported by Sakakibara, Orihata & Hayashi (1962). Cooley, Beall & Grondin (1962) were able to verify these findings, both in animal experiments and clinically, and to show by studies of microcirculation that the sequestration was due to aggregation of red corpuscles. These changes did not occur if 5 % glucose was used instead of homologous blood. Theye & Kirklin (1963), however, carefully studied 12 patients but were unable to find either sequestration or de-sequestration after priming with homologous blood.

One possibility that has been contemplated as a way of overcoming these drawbacks is to use autologous blood, which, as has been demonstrated by Wernitsch & Hirsch (1962), does not give rise to any measurable hemolysis on perfusion. However, since methods of preserving blood for such long periods have not yet been perfected, the only thing to do up till now has been to substitute the whole priming volume or part of it with other fluids and to replace blood losses with acid-citrate-dextrose (ACD) blood. A further disadvantage attending the use of homologous blood is the risk of serum hepatitis, which is proportional to the quantity used. According to Alsever & Barger (1961), this risk is 0,6 % per unit of blood.

Hemodilution

Isotonic saline solution, 5 % glucose, albumin, Dextran®, Rheomacrodex®, Hemaccel®, and other substances have been used to dilute or replace blood in the heart-lung machine. Gollan, Hoffman & Jones (1954) demonstrated on dogs with a body temperature of 3° C that it was possible to replace blood with Ringer's solution. By re-introducing the blood prior to raising the body temperature, the authors succeeded in reviving the dogs.

In bubble oxygenators with a low priming volume, Zuhdi et al., Panico & Neptune (1959) and others have entirely replaced blood with 5 % glucose with good clinical results; Long, Sanchez, Varco & Lillehei (1961) have partially, and De Wall & Lillehei (1962) completely, replaced the blood priming with Rheomacrodex. These authors employed moderate hypothermia (approx. 25° C) and a low rate of flow.

Comprehensive experiments in hemodilution have also been carried out with spinning-disc oxygenators. Since these necessarily have a higher priming volume (at least 2.5 l), not all the blood can safely be replaced, as it is inadvisable to dilute the blood in the perfusion system, i.e. machine and patient, by more than 20 % (Raison 1962). Clinical results from hemodilution in disc oxygenators with high rates of flow (2.4 - 2.8 l/min./m^2 body-surface area (BSA) and moderate hypothermia (25 - 30° C) have been reported by Raison (1962) and with high rates of flow and light hypothermia (30 - 33° C) by Hellström & Björk (1963). The usual quantity of liquid used for blood dilution is 20 ml per kg body weight (b.w.) for adults and 40 ml/kg b.w. for children, but up to 40 ml has previously been used clinically in adults (Björk, Hellström & Nordlund 1963).

During 1965 Neville, Scicchitano, Maben, Banuchi & Peacock reported successful experimental and clinical results from extra-corporeal circulation (ECC), using a disc oxygenator which was primed only with Tham or bicarbonate-buffered Ringer lactate 2.5 - 3 l. Normo- or hypothermia was used, with a hemodilution of 33 - 60 ml/kg and a flow of 50 - 80 ml/kg/min. Good results were reported in 58 patients, who did not suffer from acidosis, despite a perfusion hematocrit of 24 % on the average and a mean perfusion time of 92 minutes. These authors used as great a hemodilution as 100 - 120 ml/kg body weight on dogs with good results. Gadboys, Litwak, Ishiguro & Kahn (1965), on the other hand, showed in experiments with dogs that a hemodilution of 10 ml/kg can be carried out with a number of

different fluids without significant changes arising, while a hemodilution of 100 ml/kg produces changes which are specific for the diluting fluid. In a survey published by Paton and Rosencrantz in 1965 concerning hemodilution, it is stated that "no single perfusate has been shown to be definitely superior to all others in enough respects to warrant its universal acceptance".

B. USE OF LOW-MOLECULAR-WEIGHT DEXTRAN IN OPEN-HEART SURGERY

Low-molecular-weight colloids (Rheomacrodex®, Mw 40.000) has the property of preventing and dissolving the fresh aggregation of red blood cells, a fact which has been evidenced in a large number of investigations during the last 15 years (Thorsén & Hint 1950, Gelin 1956, Conference on the Evaluation of Low-molecular-weight Dextran in Shock, 1962). In addition, Rheomacrodex has the property of reducing the viscosity of the blood at a low rate of flow (shear rate) and should therefore be regarded as a preparation specifically for use in conditions of slow peripheral circulation of the blood and not for use as either an osmotic diuretic or a volume expander (Moore 1963).

In ECC there is often, on one hand, an aggregation of red blood cells produced by the accumulation in the serum of denaturated proteins in the boundary layer between blood and gas (Lee, Krumhaar, Fonkalsrud, Schjeide & Maloney 1961) and, on the other, low rates of flow during and after the operation (Lillehei, Lillehei, Grismer & Levy 1963). Experiences with the use of an admixture of Rheomacrodex or Rheomacrodex alone in the oxygenator have therefore been reported (Long et al. 1961, Drake, Macalalad & Lewis 1961). Reduced aggregation has been found (Long et al. 1961), improved flow (Ablaza, Raber, Blanco, Morse, Adam & Nichols 1963), increased electronegativity in the red blood cells (Bernstein, Castaneda, Evans & Varco 1962), less destruction of platelets (thrombocytes) (Cuello, Bhanganada, Mack & Lillehei 1964, Hellström & Björk 1963) and reduced hemolysis of red blood cells (Hellström & Björk 1963, Cuello et al. 1964). Among the disadvantages, increased bleeding has been noted, especially during the operation (Smith, Melrose & Bentall 1963, Breckenridge & Walker 1963), and particularly if more than 2 g per kg body weight was administered. The risk of renal damage if Rheomacrodex is given to dehydrated patients has been discussed (Lillehei et al. 1963, Arturson, Granath, Thorén & Wallenius 1964, Bergentz, Falkheden & Olson 1965). There are different opinions as to both these disadvantages.

C. ACUTE RENAL FAILURE AND OPEN-HEART SURGERY

Despite all the progress made, there still remain three great dangers in surgical interventions: shock, infection and acute renal failure (Sawyer, Sawyer & Robb 1963). The pathogenesis of tubular damage after ECC is not clear. It may be due to nephrotoxins released from the site of the trauma, tubular anoxia on account of abnormal renal hemodynamics, or the formation of casts from cell debris and/or pigment (Schuster, Kakvan, Vawter & Narter 1964). These authors also consider that the high percentage of patients with pathological urine sediment following ECC indicates that many of them have been on the verge of sustaining renal damage. Acute renal failure is considered to be functional when a reversible progressive oliguria is present with increasing azotemia, hyperkalemia and acidosis but with no microscopic tubuli changes (Attar, Borges, Cowley, Esmond, Hollingsworth & Blair 1963). If there are such changes or irreversible anuria, the damage to the tubuli is organic and is often called tubular necrosis or lower nephron nephrosis. The statements, as to the frequency of acute renal failure following ECC, vary greatly,

depending on the composition of the reported material, as the frequency will rise with increasing elements of acquired vitia (Grismer, Levy, Lillehei, Indeglia & Lillehei 1964). The mortality from acute renal failure following surgical interventions is high and figures of up to 80 % have been reported (Lutzeyer 1962). Here also the figures depend on wether cases of both functionally and organically conditioned acute renal failure have been included and on whether intensive, early treatment has been introduced (Norman, McDonald & Sloan 1964). These authors consider that renal damage progresses more quickly after ECC than after other causes of damage.

It is of great importance that the diagnosis should be made as early as possible (Sigler 1963). This requires continuous observation of the flow of urine with the help of an indwelling catheter in the bladder (Powers 1963) and checks on the patient´s degree of hydration. In cases of oliguria (which is defined in very different ways in the literature but is usually given as 350 - 450 ml/24 hours for adults or 0.20 - 0.30 ml/kg/hour) attempts have been made to differentiate between prerenal and renal causes by giving a fluid load, in order to eliminate the possibility of dehydration (Powers 1963), or a mannitol load in order to eliminate the possibility of organic renal damage (Moore 1963). Another way is to measure the osmolality or the concentration of urea in the urine and the plasma at the same time. If these quotients approach 1, then the prognosis is very unfavourable, even though there may be only a moderate amount of oliguria or none at all (Franklin & Merrill 1960, Grismer et al. 1964, Nordlund & Hamfeldt 1965). The quotient can be determined in a case of pronounced oliguria and its prognostic value is not diminished in such a case (Norman et al. 1964). Measuring only the rise in serum creatinine or NPN (non-protein nitrogen) also provides good possibilities of making a prognosis but does not give such rapid information (Grismer et al. 1964). An endogenous creatinine clearance of < 5 ml/min also indicates acute renal damage (Balslöv & Jörgensen 1963), while the PAH clearance may give very misleading values in cases of changed hemodynamics (Josefsson 1965, Boba, Gainor & Powers 1962), if the PAH concentration in the blood of the renal vein is not determined at the same time (Josefsson 1965).

The classification of the degree of renal damage following ECC is given in most cases as either acute renal failure or none at all, but Yeh, Brackney, Hall & Ellison 1964 have divided the patients into the following groups, according to their postoperative renal function:

"Group I No renal damage. BUN below 30 mg% at all times. Serum K^+ within normal range throughout. Urinary output above 600 cc daily for adults, and corresponding values for children on the basis of body surface area.

Group II Borderline damage. Elevation of BUN above 31 mg% on at least 2 consecutive days but not above 60 mg%. Otherwise no difference from group I.

Group III Moderate renal damage (renal tubular acidosis). Steadily increasing BUN of above 60 mg% and some as high as 130 mg% without oliguria, except during the immediate postoperative period.

Urinary output was normal or increased to 4000 cc/per day. Serum K^+ was within normal range or elevated only transiently.

Group IV Severe renal damage (renal tubular necrosis). Rapidly rising BUN with peak of 130 to 300 mg% and serum K^+ of above 6 mEq/l. Urinary output was below 400 cc on at least 2 days, no diureses on fluid load."

D. USE OF MANNITOL IN OPEN-HEART SURGERY

Mannitol, the reduced form of mannos, a sugar alcohol with five carbon atoms and a molecular weight of 182, is not metabolized in the body and penetrates the cell membranes very slowly but is equilibrated quite rapidly in the extra-cellular space. For this reason, it was used during the 1930s and 1940s to measure this space (Elkinton 1947). Since Selkurt pointed out the possibilities of mannitol as an osmotic diuretic in 1945, it has found more and more uses. It has been used in surgery to lower the intracranial pressure; to differentiate between functional and organic tubular damage; as a prophylactic against renal damage in traumatic or hypovolemic shock; as a supplement to the priming volume in ECC; and as a prophylactic or therapeutic agent in oliguria after surgical interventions, transfusion reactions, hemolytic crises and burns (according to a summary made by Hallwachs in 1965, which also contains a survey of the history, literature and physiology of mannitol). The present opinion, judging from the surveys that have been made (Moore 1963, Maloney 1965), is that mannitol is excellent for a differential diagnosis between functional and organic renal damage but that it has no effect in cases of manifest tubular damage. Opinions are sharply divided as to whether the prophylactic induction of osmotic diuresis with mannitol has a protective effect against renal damage. In the very comprehensive literature about mannitol the number of publications that confirm the existence of this protective effect is approximately the same as those which deny it (Maloney 1965).

The renal plasma flow and the glomerular filtration rate always fall during anesthesia, surgical interventions and ECC (Lundberg 1964, Grismer et al. 1964), but mannitol is thought to be able to prevent the fall in RPF (Kahn, Cerny, Lee & Sloan 1965).

The experiments on dogs carried out by Steenburg, Marinho & Santiago (1965) give a probable explanation for this finding. They showed that both the re-absorption and the interstitial concentration of urea in the renal medulla and papillae diminish with mannitol diuresis, owing to the fact that the concentration of urea in the urine is reduced when it is diluted. After surgery and other traumata there is often hypotonia with reduced GFR and an increased concentration of urea in the blood. When re-absorption of urea takes place, the viscosity of the blood in the vasa recta increases and the renal circulation deteriorates further. The authors consider that this is the explanation of why even short periods of hypotonia may be deleterious for the kidneys, even though the circulation in the rest of the body has been normalized. In experiments on dogs this vicious circle could be broken or prevented from arising by the administration of mannitol, which is a strong argument in favour of the clinical use of mannitol.

E. MORTALITY AFTER OPEN-HEART SURGERY

The figures reported for mortality following open-heart surgery cannot be reliably compared as between different clinics and periods of time. This is due, amongst other things, to differences in the selection of patients and in the technique employed.

In Table 1 a small number of mortality reports have been brought together as an example. There are differences between all the reported materials, especially as regards age, the composition of the diagnoses and the preoperative status of the patients but also between the choice of oxygenator, prime and perfusion times. Very low mortality figures for combined procedures have been reported by Starr and Kirklin separately. Even when mortality figures are reported from the same diagnosis group, preoperative factors must be taken into account, as has been shown

by Leachman, Hallman & Cooley (1965), who report mortalities of 10 % or 31 % in Fallot´s tetralogy, if the preoperative Hb value lies below or above 18 g%.

The mortality is usually reported as operative (death on the operating table or during the first 24 hours after the operation), postoperative (1 - 5 and up to 10 days after the operation) or late death (after 10 days). In other cases "late death" means death after the patient has left the hospital or after 30 days. Norman et al. (1964) found that 50 % of deaths occurred within 24 hours after the operation and 65 % within 48 hours.

F. USE OF COMPUTERS IN MEDICINE

The number of fields in medicine in which modern data-processing technique is in use is rapidly increasing (see, for instance, the Symposium on the Applications of Digital Computers, 1964). According to Spencer & Vallbons (1965), the last six years´ work has shown that the following fields will probably use computers in the future:

1. Medical diagnosis.
2. Case records
3. Laboratory analyses and tests of physiological function.
4. Patient monitoring.
5. Hospital communications.
6. Utilization of hospital services and facilities.

Schwichtenberg (1965) points out that at present we base our diagnoses and prognoses on measurements made in a static state, while the patient is in fact subject all the time to continuous changes, for example, aging. For correct diagnoses we shall in future need curves for different processes, from which extrapolations can be made.

During the last few years an increasing number of authors has used data processing to analyse the influences of various factors or groups of factors on different postoperative parameters in open-heart surgery. Thus Yeh et al. (1964) and Norman et al. (1964) have used this technique to make statistical analyses of the influence of a large number of peroperative factors on the postoperative renal function following ECC. No account was taken of the possible influence of the patient´s preoperative status.

CHAPTER II

MATERIAL AND CLINICAL TREATMENT

A. CLINICAL MATERIAL AND PRINCIPLES OF SELECTION

The investigation was carried out on 191 patients operated on with the aid of ECC at the Thoracic Surgery Clinic, University Hospital, Uppsala, between October 1962 and the end of April 1965. Normally, the patients were selected for operation according to the following general indications.

1. Heart volume

Patients with congenital or acquired aortic stenosis, Fallot´s tetralogy or tumor cordis were operated on, even if the heart was of normal size (as measured by X-ray methods). Patients with other defects were operated on only when the heart was enlarged. Angina pectoris (coronary sclerosis with localized stricture) was not operated on if the heart was enlarged. Acquired lesions in the aortic cusps were only operated on in exceptional cases if the heart volume exceeded 1000 ml per sq.m. of body-surface area (BSA).

2. Gradient

Isolated aortic stenosis was operated on if the resting gradient (with normal systemic blood flow) exceeded 50 mmHg.

3. Insufficiency

Isolated aortic or mitral insufficiency was operated on only when the degree "4" (later defined) was diagnosed by aortography or left ventricular cardiography, respectively.

4. Shunt

Atrial or ventricular septal defects were operated on if the shunt at rest was calculated to exceed approximately 30 % (for example, pulmonary flow 6 l/min, systemic flow 4 l/min). Such defects were not operated on if the patients had equilibrated pressures between the right and left ventricle and/or a right to left shunt.

5. Age

Patients over sixty years old were operated on only in exceptional cases.

In addition, the following special principles of selection were applied in choosing patients for the present investigation.

Only patients over the age of fourteen or weighing more than 50 kg were selected. (As an exception, two children weighing about 30 kg each were included because they were operated on with the aid of the disc oxygenator used for adults.)

The same heart-lung machine (Pemco-Mark II) was used in all cases. It was equipped with the (Kay-Cross) disc oxygenator or alternatively, during the last year of the investigation, with a bubble oxygenator of the Rügg-Kyvsgaard pattern. The choice of oxygenator was made on the principles described in the next paragraph.

The disc oxygenator was used in the following cases:

(1) Cases in which the perfusion time was calculated to exceed 90 min.

(2) Hypothermia was required. (The bubble oxygenator used had no heat exchanger at that time.)

(3) The body-surface area of the patient was 2 sq.m or over.

(4) In all cases in which complicated lesions were operated on, such as combined lesions in the aortic and mitral valves.

The disc oxygenator was preferred when patients with Fallot´s tetralogy or aortic lesions with massive calcifications or with large heart volumes were operated on. Because of the difficulty of obtaining blood of certain groups, exceptions were made to these principles in a few borderline cases.

The bubble oxygenator was considered suitable in the following types of case:

(1) Ostium primum or ostium secundum defects (the latter type was, however, generally operated on in moderate hypothermia and with inflow occlusion).

(2) Ventricular septal defects.

(3) Mitral insufficiency or combined mitral lesion.

(4) Most cases of aortic insufficiency.

(5) Congenital aortic stenosis.

On these principles, 59 patients were operated on with the bubble oxygenator and 132 with the disc oxygenator.

Priming volume. At first 3-4 bottles (450 ml) (each bottle contained 30 ml of 5 % glucose and 20 mg of heparin (Vitrum) 1 mg = 100 IU.) of freshly drawn heparinized blood (2 hours) were used in the bubble oxygenator. Subsequently, consistently greater hemodilution was introduced until (for the last six months in 20 consecutive cases) blood was entirely replaced by the following priming fluid: Rheomacrodex® 1 g/kg body weight (b.w.) (10 % solution in 5 % dextrose in water), 200 ml of 15 % mannitol, 300 ml of Aminosol-glucose® and 5.5 % glucose until the total volume in the oxygenator was 1600 ml.

The disc oxygenator was primed with a total volume of 3600 to 3800 ml. The distribution of different primes according to the type of operation can be seen in Table 3, where B denotes a prime with freshly drawn heparinized blood only, R the addition of 1000 ml Rheomacrodex, M the addition of 500 ml of 15 % mannitol and "Mixed" principally a prime consisting of Rheomacrodex 1 g/kg b.w. + 200 ml of mannitol + 300 ml of Aminosol glucose + 5.5 % glucose to a total diluted volume of 1500 ml.

During the first three months of the investigation all patients were operated on with the addition of 1000 ml of Rheomacrodex in the oxygenator. Patients with Fallot's tetralogy were often also given an addition of Rheomacrodex. For the remainder, a random distribution of the different primes was aimed at. However, from the statistical point of view the material cannot be considered as having been chosen at random.

B. CLINICAL TREATMENT

1. Preoperative measures

The patients were not allowed food or fluids for the last twelve hours before the operation. A duodenal tube was inserted preoperatively as a matter of routine.

2. Anesthesia

Premedication was carried out in all cases with promethasine chloride (Lergigan®) in combination with mebumal sodium (Nembutal®) and atropine. After a period of breathing pure oxygen, anesthesia was induced (in two-thirds of the cases) with thiopenthone (Penthotal®) in a 2.5 per cent solution and endotracheal intubation was carried out under succinylcholine (Celocurine®) relaxation. Continued muscular relaxation was obtained by means of a mixture of nitrous oxide and oxygen (here called "balanced anesthesia"), in some cases combined with halothane (Fluothane®) or metoxyflurane (Penthrane®), administered through the respirator. During ECC anesthesia was continued in the same way, but nitrous oxide was excluded. In cases in which postoperative respirator treatment was not indicated, decurarization was obtained by means of synstigmine (Prostigmin®), after injection of atropine.

In one-third of the cases (during the last 8 months), this procedure was replaced by a modified neurolept analgesia. Both induction and continued anesthesia

were obtained with phenoperedine (Lealgin®) and muscular relaxation with d-tubocurarine (Tubarin®). During ECC only pure oxygen was administered in the oxygenator. All the lastmentioned cases received postoperative respirator treatment. In all cases ventilation during operation was carried out with an Engström respirator in a non-rebreathing system and with a volume calculated according to the body-surface area, age and sex.

3. Perfusion technique

Priming the oxygenator. The blood, with any possible additions, was poured into the oxygenator some 30-60 min before the commencement of the ECC and oxygenated for a period of 1-2 min.

Ventilation during ECC. The gas in the disc oxygenator was changed at a disc rotation speed of 120 revolutions per min. Ventilation was obtained with pure oxygen, the flow of which was regulated according to the carbon-dioxide tension in the arterial blood of the patient, usually 5-6 l/min. In the bubble oxygenator an oxygen flow of 1.5-2 l/min per litre of blood flow was used. When Fluothane or Penthrane was used, these gases were introduced into the oxygen flow of the oxygenator. During total perfusion the lungs of the patient were ventilated with 2 l of air per min administered by the respirator at the rate of ten strokes per min. A slight positive end-expiratory pressure was used.

Flow rate and perfusion pressure. During total perfusion a blood flow of 2.2-2.4 l/sq.m BSA/min was maintained if possible, that is, 50-60 ml/kg b.w./min. The arterial perfusion pressure (measured by a catheter inserted into the arteria brachialis or femoralis) was maintained at about 90-110 mm Hg, if possible. At a pressure lower than 80 mm Hg, extra blood was added to the machine or the patient while perfusion was in progress. When carrying out perfusion with the bubble oxygenator without blood being added to the priming volume, one bottle of blood was invariably added every 15 min. The first three of these had an addition of heparin, ACD blood being used thereafter.

Body temperature during ECC. During total perfusion with the disc oxygenator the body temperature was reduced with the aid of the oxygenator's heat exchanger. At the end of total perfusion the temperature was raised to 35-37° C. In more than half the cases the esophageal temperature did not fall below 32° C. In certain cases the temperature was reduced below 30° C. At that time, there was no heat exchanger for the bubble oxygenator, but the temperature was spontaneously reduced to approximately the same extent as with the disc oxygenator during total perfusion, while the temperature generally rose spontaneously during the postoperative phase, allthough surface warming had to be utilized in a few cases.

4. Peroperative monitoring

As soon as anesthesia was induced, continuous monitoring was commenced of the ECG, arterial blood pressure and central venous pressure. This monitoring was continued during the first postoperative phase. The whole arterial blood pH, pCO_2, HCO_3 and pO_2 were monitored by taking test samples from the patient throughout the operation: twice before ECC; at ten-minute intervals during ECC; immediately after ECC and also 1-3, 3-5 and 5-10 hours after ECC. Samples were taken from the disc oxygenator before ECC (after oxygenation of the prime). Hemoglobin and hematocrit were measured in all samples, white blood cells and thrombocytes were counted before, during and after ECC in one sample from each period.

Blood losses during the operation were measured in suction bottles and by weighing compresses and swabs and the losses were continuously replaced with ACD blood.

After ECC the heparin given before the perfusion was started (3 mg/kg b.w.) was neutralized by the same amount of protamine. Then tests were made to ascertain that the blood-coagulation time was normal.

The body temperature was continuously measured both in the esophagus and the rectum. The production of urine was measured in about 140 cases by means of an indwelling catheter. The urine was collected separately in four portions during the day of operation: before ECC, during ECC, after ECC until the end of the operation, and in the postoperative ward from then until next morning. The concentrations of K^+, Na^+, Cl^-, phosphate, creatinine and urea were determined in each portion.

5. Postoperative care

In the postoperative phase continued ventilation with the Engström respirator was employed in the great majority of cases. This was carried out either via a tracheal cannula introduced by tracheotomy (when it was considered that a longer period of respirator treatment was indicated) or via the endotracheal tube used during the operation.(when it was considered that the treatment could be concluded within a period of 24-48 hours).

Blood losses via the drainage tubes were replaced by ACD blood during the immediate postoperative period but later so that the hemoglobin and hematocrit were kept above 10 g% and 36 % respectively. Postoperatively a central venous pressure, measured with a catheter in the superior vena cava or right atrium, of between 5 - 15 cm of water was maintained, if possible.

Fluid was added according to the following schedule:

Day of operation:	600 ml/sq.m BSA
Day 1:	900 ml/sq.m BSA
Day 2:	1200 ml/sq.m BSA

Depending on the condition of the patient, larger quantities of fluid were given per os and less intravenously. Losses from the duodenal tube were replaced in addition to the fluid added according to the schedule above. All the patients were weighed daily. Where there was a tendency for the postoperative weight to increase, the fluid intake was restricted and diuretics were added to the digitalis treatment that almost all the patients received.

Besides the urine measurements and the tests started during the operation and continued for two days postoperatively, daily tests were made of serum electrolytes and blood status. Pulse rate and arterial blood pressure were measured at frequent intervals and the ECG was continuously monitored, if necessary. Chest X-ray films were made daily and bacterial culture samples from the incision and the blood were taken several times a week. Antibiotics were administered prophylactically to all cases. Sodium, potassium, albumin, etc. were added according to the losses and respective serum levels measured. The patients were mobilized as soon as possible, according to their condition; all uncomplicated cases were allowed to stand up on the morning after the operation.

C. CHANGES IN TECHNIQUE DURING THE INVESTIGATION PERIOD

1. Infection prophylaxis

The first 34 cases received 2 g of Chloromycetin daily for one week after the operation. The following 21 cases also received 30 million I.U. of benzyl penicillin via a catheter in the superior vena cava for 4-6 days and thereafter penicillin per

os (for six months). The last 136 cases also received 20 million I.U. of penicillin in the oxygenator. Postoperatively the treatment was the same as for the preceding 21 cases, as stated above.

2. Anesthesia

In 81 cases halogenated-inhalation anesthetics were used during the whole operation; in 15 cases only during ECC. Fifty-seven cases were anesthetized instead with phenoperidine, while in the remainder of the cases "balanced anesthesia" was employed, all in accordance with the technique described earlier.

3. Impaired postoperative renal function

During the last nine-tenths of the investigation period, cases with postoperative oliguria (less than 15 ml of urine per hour), in spite of an adequate degree of hydration and normal central venous pressure, were treated with mannitol. One or sometimes two test doses of the 15 % solution were first administered, and, if the desired osmotic diuresis resulted within the next few hours, the diuresis was maintained by an intravenous mannitol drip.

4. Postoperative low cardiac output

During the last 6 months this syndrome was treated with Isoprenalin® or hydrocortisone (doses of 1-2 g), instead of the therapy practised earlier, using sympathicomimetics with peripheral vaso-constrictory effects (α-receptor stimulation).

D. SUMMARY OF PATIENT MATERIAL

The different series of analyses (to be reported later) were based either on all the 191 patients included in the material, or on the 181 patients left when the 10 patients who died within 24 hours of the operation, and for whom the data from the day of operation were missing were excluded. The material was divided according to diagnoses (Table 2) and according to the types of operation performed (Table 3). The distribution of sex, age and some other preoperative factors can be seen in Tables 4 and 5.

Besides the patient material described above, which formed the basis for the analyses, the validity of the forecast indices described in Ch. IV were tested on all or parts of another patient material (74 patients), operated upon before or after the period of investigation. This material is not otherwise specified but was selected and treated as stated above.

CHAPTER III

REGISTRATION AND STATISTICAL TREATMENT OF DATA

A. RECORDING DATA FOR COMPUTER TREATMENT.

The available information for each patient that had a bearing on the investigation was assembled in list form for data-processing.
The following information groups were tabulated:

1. Preoperative factors (background)

(a) General: sex, age, height, weight, height minus weight and body-surface area.

(b) Patient's illness: congenital and acquired, specified diagnosis and the diagnoses assembled into five "diagnostic groups".

(c) Course of illness: duration of illness, duration of symptoms before the operation, duration of incapacity for work, commencement of permanent atrial fibrillation, digitalization time, number of known embolisms and digitalis and/or diuretic preoperative medication ("preoperative heart failure").

(d) General preoperative investigation: systolic-diastolic arterial blood pressure, relative heart volume, work-load test, left and/or right ventricle hypertrophy or "other important ECG changes", preoperative laboratory blood tests, preoperative 24-hour urine volume and creatinine clearance.

(e) Special preoperative investigation:
Diagnostic group I (predominant aortic lesion): aortic gradient at rest, degree of aortic insufficiency, systolic and mean pressure in pulmonary artery at rest, preoperative flow at rest and end-diastolic pressure in left ventricle.
Diagnostic group II (predominant mitral lesion): degree of mitral valve insufficiency, systolic and mean pressure in arteria pulmonalis at rest and systolic pressure at work, PCV pressure at rest and during work, systemic blood flow at rest and end-diastolic pressure in left ventricle.
Diagnostic group III (shunts except Fallot's tetralogy): systolic and diastolic pressure in right ventricle, systolic and mean pressure in arteria pulmonalis, PCV at rest, systemic and pulmonary blood flow and left to right shunt in litre/min.
Diagnostic group IV (Fallot's tetralogy): systolic pressure in right ventricle at rest and during work, systolic pressure at rest in pulmonary artery, pulmonary gradient at rest and O_2 saturation in arterial blood at rest and during work.
Diagnostic group V: no complete or representative pressure figures were available.

(f) Pressure measurements made during the operation before surgical intervention according to diagnostic group: aortic gradient, pulmonary gradient, systolic and diastolic arterial pressure, systolic and diastolic left and right ventricle pressure, maximum and minimum pressure in left atrium.

2. Peroperative factors

(a) General: specification of surgical intervention performed, different types of operative procedures assembled into seven "operation groups", type of anesthesia, disc or bubble oxygenator, composition of prime, operation time before and after ECC and time of entire operation, weight change during operation, size of Starr ball-

valve prosthesis inserted, number of shocks for conversion of ventricular fibrillation and complications resulting from the operation.

(b) Data relating to the perfusion: overall perfusion time, duration of total perfusion, arrest, left and right coronary perfusion, measured blood flow and lowest temperature during total perfusion in esophagus.

(c) Perfusion checks: acid-base balance, hemoglobin measurements and blood cell counts, degree of hemolysis and the monitoring of arterial blood pressure and ECG.

(d) Fluid balance during operation: blood loss and blood replaced, urine quantity, quantity of intravenously administered fluid.

(e) Drugs administered: epsilon-amino-capronic acid, $NaHCO_3$, tris-hydroxy-methyl-amino-methane (Tham or Tris), mannitol, fibrinogen.

3. Postoperative factors

(a) General: type of antibiotic prophylaxis given, sinus rhythm after operation, postoperative heart-rhythm disturbances, falls in blood pressure, type of therapy in cases with postoperative low cardiac-output syndrome, re-operation resulting from hemorrhage, acid-base balance.

(b) Postoperative pressure measurements (immediately after ECC): the same as stated under 1 (f) above.

(c) Continued monitoring and postoperative care during the remainder of the day of operation or longer, as described in chapter II, section 5 "Postoperative care".

4. Result factors

Mortality within 30 days, postoperative renal function.

Comments

Ad (1) Preoperative factors:

Only unmistakable cases have been called congenital, while doubtful cases (for instance, cases of calcified aortic stenosis) are considered among the acquired defects.

The diagnoses were based on the preoperative investigations and in a few cases also on the operative findings and were arranged in five groups, as under 1 (e) above and in Table 2.

Diagnostic group V consists of miscellaneous diagnoses, such as tumor cordis, angina pectoris and aortic aneurisms, in which the oxygenator was connected for partial or total perfusion.

The relative heart volume was measured in a sitting posture in ml/sq.m BSA, according to the standard radiological method described by Jonsell (1939).

Where there was regular preoperative therapy with both digitalis and diuretics for at least one week, for lack of reliable criteria, it was considered that a certain preoperative heart failure existed. Accordingly, the patients were registered as 1 = no preoperative medication, 2 = preoperative digitalis and 3 = digitalis + diuretic treatment.

Aortic insufficiency was determined radiologically by aortography and divided into four groups, as described by Cullhed (1964):

Grade I = subvalvular contrast leakage in diastole.
Grade II = incomplete diastolic contrast-filling of left ventricle.
Grade III = the entire left ventricle is seen to be contrast-filled, but the contrast density is thin, considerably thinner than in the ascending aorta.
Grade IV = as grade III, but the contrast density is more similar to that in the aorta.

The degree of mitral insufficiency was also determined by radiological methods (left ventricular cardiography) and recorded as follows (only if extra systoles were not present):

Grade I: never more than incomplete, very thin contrast-filling of the left atrium.
Grade II: complete, possibly thin, contrast-filling of the left atrium, when the descending aorta was filled with contrast fluid all the way or almost all the way down to the diaphragm.
Grade III: complete filling of left atrium, when the contrast fluid reached the middle of the arcus aortae.
Grade IV: complete filling of left atrium, when the contrast fluid had reached the root or the middle of the ascending aorta.

This classification was made according to Malers (1963), but the number of degrees of insufficiency was reduced from his seven to four.
The right, left and transseptal catheterizations were performed according to standard methods (see Cullhed 1964 and Cullhed & Malers 1966), as were the calculations of shunts, blood flow, etc.

Criteria for ECG classification *

Method The following leads were recorded: I, II, III; aVR, aVL, aVF; V_1 - V_6 or V_1, V_2, V_4, V_5, V_7. A conventional directwriting ECG apparatus was used (Mingograf 42 or 81, Elema-Schönander, Ltd., Stockholm).
Atrio-ventricular conduction time and QRS duration were measured in leads I-III. The QRS amplitude was measured either as deepest S in V_1 or V_2 plus highest R in V_5 or V_6, or as largest total QRS in any of V_1 to V_7, whichever gave the largest value. The last ECG recording before operation was used, if technically satisfactory.

Evaluation. The ECG was evaluated according to generally accepted principles. The following borderlines were used:
a-v block of the first degree at P-R or P-Q equal to or more than 0.22 sec at heart rate 70; bundle branch block at QRS duration equal to or more than 0.12 sec at heart rate 70; prolonged activation time as 0.06 sec or more in any of leads V_4-V_7 (left ventricle), or as 0.04 or more in any of leads V_1-V_2 (right ventricle); high QRS amplitude at 4.0 mV or more at age 30 years.

ECG signs of left ventricular hypertrophy were evaluated in three categories (absent, moderate or pronounced), in the first place from the combined effect of QRS amplitude, "left ventricular activation time" and ST-T depression in left precordial leads (taking into account any digitalis medication), in the second place from R vector orientation and QRS duration.

ECG signs of right ventricular hypertrophy were evaluated in three categories (absent, moderate or pronounced), in the first place from abnormal QRS distribution in precordial leads, "right ventricular activation time" and ST-T depression in right precordial leads (taking into account any digitalis medication and ST depression in left precordial leads). Ventricular hypertrophy was classified as absent in the presence of bundle branch block.

*(in collaboration with Prof. G. Ström)

"Other ECG changes". A classification of "infarction" was based on the presence of abnormal Q or QS, ST elevation and abnormal T, taken as additional evidence; the isolated finding of abnormal (negative or flat) T was classified as "myocardial affection"; abnormal QRS splitting or QRS amplitude distribution (without bundle branch block) was classified as "intraventricular disturbance". Such ECG changes and others were also classified as moderate or pronounced (Table 5).

Criteria for work-load test classification

Method and evaluation

A work-function test according to Sjöstrand and Wahlund was performed. ECG, heart rate, arterial blood pressure (auscultatory cuff method) and maximum expiratory flow were first recorded at rest. An orthostatic test (8 min passive standing) was then performed, followed by a work test with gradually increased work loads, with a duration of 6 min at each load. The loads were chosen so that it would be possible for the patient to work with at least two and at most three or four different loads. The ECG was monitored or recorded continuously and the heart rate, respiration rate and arterial blood pressure were measured repeatedly at each load. The patients were also supervised clinically according to the symptoms and signs from the circulation and respiration. The work test was interrupted either when the heart rate reached approximately 170 beats per min or when abnormal signs or symptoms were repeated or heterotopic ventricular extra systoles or other remarkable arrhytmia, marked ST depression with disformation, AV or IV conduction disturbance, a fall or a very steep rise of arterial blood pressure, marked or otherwise remarkable tiredness, dyspnoea, chest pain or dizziness, etc. The highest work load actually achieved for at least 4 min was taken as an index of the "work capability", irrespectively of the type of limitation. No noteworthy complications occurred during the work tests. (The principles employed are described by Wahlund 1948).

Laboratory tests (hemoglobin, hematocrit, white blood cells and platelets, serum electrolytes (K^+, Na^+, Cl^- and HCO_3^-), preoperative creatinine content in blood and urine and non-protein nitrogen (NPN), were determined in single tests according to the normal hospital routine methods (de Verdier & Killander 1963).

The preoperative quantities of urine recorded represent the mean value of three successive 24-hour periods. All measurements of urine were given to the nearest whole number divisible by 5.

Preoperative weighing was carried out on the same scale, with the patient naked.

Data for body-surface area were taken from a nomogram of height and preoperative weight.

Preoperative pressure measurements (during operation before ECC) were made by direct needle puncture and calculated from Mingograf tracings.

Other preoperative data were obtained either from the hospital records or from the patients.

Ad (2) Peroperative factors

Like the diagnoses, the operative procedures have been arranged in "operation groups", as specified in Table 3. (The same patient may be related to several "diagnostic groups" but to only one "operation group".)

Anesthesia. The patients have been arranged in four groups, as specified in chapter II, section B (2), namely, "balanced anesthesia", halogenated-inhalation anesthetics only during ECC, halogenated-inhalation anesthetics during the whole operation and anesthesia with phenoperidine. The use of the disc or bubble oxygenator and the composition of the priming volume have been specified in chapter II. The operation time was calculated from the onset of anesthesia until the commencement of ECC, time under ECC and from ECC until end of narcosis. The total operation time is given to the nearest 15-minute period. The entire perfusion time has been divided into the time for total and partial perfusion, and given in minutes. The time for aortic cross-clamping is given in relation to the length of the right and left coronary perfusion. The duration of hypothermic arrest was noted as a total, though 3 min of coronary perfusion were given for every 15-minute period of hypothermic arrest.

The size of the ball valves inserted was recorded from the manufacturer's numbering (Starr-Edwards). The blood flow was given in the form of a mean value during total perfusion.

Complications during operation were recorded as follows:
(1) none; (2) slight or moderately severe complications and (3) severe complications (assessment afterwards, from results obtained).

Heart rhythm after surgical intervention: This was divided into three groups:
(1) no disturbance of rhythm, (2) slight or moderate disturbances (for instance, atrial fibrillation both before and after operation, transient total atrioventricular block or periods of extra systoles (ES)), and (3) severe permanent or deleterious arrhythmia (such as total block, frequently repeated or irreversible ventricular fibrillation).

Length of periods of low arterial-blood pressure. The extent of the drop in the systolic arterial-blood pressure (see chapter II), both under 80 mmHg and under 100 mmHg, was noted to the nearest 5-minute period, using the following time-scale - 10, 20, 30, 45 and 60 min; 1-3, 3-6 and more than 6 hours - for the following periods: during the operation, before, during and after ECC and during the remainder of the day of operation.

The degree of free plasma hemoglobin in the patient's blood immediately after ECC was measured according to a standard colorimetric method (modified Crosby-Furth technique) and given in mg%. Arterial-blood measurements of pH, standard HCO_3 and pCO_2 were measured by the micro-Astrup technique and pO_2 with an oxygen electrode (Hilty & Meissl 1966).

When judging bacterial culture in the blood sample taken from the oxygenator after ECC, results showing a "contaminated sample" were considered as a negative culture.

The coronary-perfusion technique was further developed during the period of this investigation. During the first part it was given by means of metal pipes fitted with handles, later by plastic tubing. No measurements of the actual coronary flow were made, but the ECG monitoring gave rapid and valuable information as to the adequacy of the coronary perfusion. However, this information could not be transformed into figures, and therefore only the length of the coronary perfusion was noted and given in minutes.

The number of alternate-current (AC) or later direct-current (DC) shocks necessary for converting ventricular fibrillation after ECC was recorded.

The rest of the peroperative factors have been described in Chapter II and were noted numerically.

Ad (3) Postoperative factors

All postoperative factors were obtained by methods described above or in Chapter II. The electrolyte values in both serum and urine were determined, as in other laboratory tests, by means of single tests, according to the current standard hospital method. The accuracy of the results was considered sufficient for the purpose of day-to-day comparison between different groups of patients. The sampling technique was not changed during the investigation period. Automatic analysis control was used in the hospital's main laboratory, providing, among other values, the daily spread in the analysis results.

Ad (4) Result variables

Mortality. For patients dying within 24 hours after the intervention, preoperative factors only were taken into account. For others, all the factors were used.

Postoperative renal function. The patients were divided into three groups according to the specification in Chapter VI. All the factors listed above were used.

Ad (1-3) Principles for supplementing data

Preoperative data were supplemented by insertion of mean values for the whole material or for the operation groups.

Per- and postoperative data: in a series of determinations, missing data were supplemented by insertion of interpolated or extrapolated values.

B. STATISTICAL METHODS

Notation:

Number of cases: n

Mean: $M = \bar{X} = \frac{\sum X_i}{n}$

where X_i denotes the i^{th} case.

Standard deviation,

$$SD = \left(\frac{\sum (X_i - M)^2}{n - 1} \right)^{\frac{1}{2}}$$

Standard error of the mean, σ_M or

$$SE = \frac{SD}{n^{\frac{1}{2}}}$$

Standard error of the difference between two means, $\bar{x}$ and $\bar{y}$:

$$SE_{\bar{x}-\bar{y}} = (SE_{\bar{x}}^2 + SE_{\bar{y}}^2)^{\frac{1}{2}}$$

Standard error of the difference between two percentages, p_1 and p_2:

$$SE_{p_1-p_2} = \left(\frac{p_1 \cdot (100 - p_1)}{n_1} + \frac{p_2 \cdot (100 - p_2)}{n_2} \right)^{\frac{1}{2}}$$

Regression analysis

Correlation analysis. The correlation coefficient, r, of x and y is defined by the expression:

$$r = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\left(\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2 \right)^{\frac{1}{2}}}$$

where $\bar{x}$ and $\bar{y}$ denote the means for the x and y series respectively. The residual value for an individual (i) is defined as the observed y value minus the predicted y value (cf. p. 26).

The partial correlation coefficient between x and y with z held constant:

$$r_{xy.z} = \frac{r_{xy} - r_{xz} r_{yz}}{\left((1 - r_{xz}^2)(1 - r_{yz}^2) \right)^{\frac{1}{2}}}$$

The residual variance is defined as;

$$\frac{\sum \text{residuals}^2}{n - k - 1} = \frac{\sum (y_i - b_o - b_1 x_i^{(1)} - b_2 x_i^{(2)} \ldots b_k x_i^{(k)})^2}{n - k - 1}$$

where b_0, b_1 ... b_k denote the estimated coefficient values. The multiple correlation coefficient, R^2 is

$$R^2 = 1 - \frac{(n - k - 1) \cdot \text{residual variance}}{\sum (y_i - \bar{y})^2}$$

Significance tests

1. In testing the difference between two percentages: the χ^2 test with one degree of freedom was used. Yates' correction was applied.

2. In testing differences between means, the following approximately normally distributed critical ratio was formed:

$$CR = \frac{\bar{x} - \bar{y}}{SE_{\bar{x}-\bar{y}}}$$

3. In testing whether the regression coefficients differed from 0, the method described by Cramér (1946) and Hald (1948), was used:
A t value was produced from the expression: $\frac{b_j}{SE_{b_j}}$

4. In testing whether a correlation coefficient differed from 0, the following ratio was produced:

$$\frac{r}{(1 - r^2)^{\frac{1}{2}}} (n - 2)^{\frac{1}{2}}$$

which - if the true correlation was zero - was distributed like Student's t, with n-2 degrees of freedom.

Significance levels:

The term "significant" is used in accordance with the following convention. If an observed difference between two means is of such magnitude that the probability, P, of obtaining a difference at least as great as the observed value is greater than 0.05 (where the null-hypothesis is assumed to hold), then that observed difference is said to be non-significant.

If $0.01 < P < 0.05$, the difference is said to be (probably) significant and is marked *.

If $0.001 < P < 0.01$, the difference is said to be significant and is marked **.

If $P < 0.001$, the difference is said to be (highly) significant and is marked ***.

Confidence intervals. For percentages and differences between percentages, the confidence intervals (95 per cent level) were calculated in some instances by adding ± 2 SE to the percentage or difference.

Multiple regression analysis used in the present study

For a series of n patients we wish to study the relation between a dependent variable, y, called the regressand, and a set of explanatory variables, $x^{(1)}$ ..... $x^{(k)}$, called regressors. The regressand may be an alternative variable in which y = 1 means "dead" and, y = 0, means "surviving 30 days after operation". The k regressors $x^{(1)}$. $x^{(2)}$ ... $x^{(k)}$ may be heart volume, age or sex.

In order to study the relation between the y and x variables, a type of equation must first be laid down. Individual numerical values must also be available for each variable. In the present work equations of the following form have been studied:

$$y = b_0 + b_1 x^{(1)} + b_2 x^{(2)} + \ldots\ldots\ldots b_k x^{(k)}$$

where b_0, b_1, b_2 ... b_k are the coefficients which are to be estimated. In estimating these coefficients the principle of least squares has been applied. This principle means that we seek values of coefficients which are constituted in such a way as to yield the smallest possible sum from the following expression:

$$\sum(y_i - b_0 - b_1 x_i^{(1)} - b_2 x_i^{(2)} \ldots\ldots b_k x_i^{(k)})^2$$

If this expression is treated in a purely mathematical fashion, as a maximum - minimum problem we obtain a general solution with the aid of the following k + 1 linear equations in the k + 1 unknown coefficients:

$$\begin{cases} \sum y = b_0 n + b_1 \sum x^{(1)} + \ldots + b_k \sum x^{(k)} \\ \sum y\, x^{(1)} = b_0 \sum x^{(1)} + b_1 \sum x^{(1)} x^{(1)} + \ldots + b_k \sum x^{(k)}\, x^{(1)} \\ \sum y\, x^{(2)} = b_0 \sum x^{(2)} + b_1 \sum x^{(1)} x^{(2)} + \ldots + b_k \sum x^{(k)}\, x^{(2)} \\ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \\ \sum y\, x^{(k)} = b_0 \sum x^{(k)} + b_1 \sum x^{(1)} x^{(k)} + \ldots + b_k \sum x^{(k)}\, x^{(k)} \end{cases}$$

corresponding to X´Y = X´XB in matrix notation.

Here $\sum y$ stands for the sum of all individual y values and $\sum y\, x^{(1)}$ the sum of all individual products of $y\, x^{(1)}$ etc.

The principle of least squares has been described in detail by Cramér (1945) and Hald (1948), who also explain the method of calculating SE for the coefficients.

Predicted value

The y value for an individual (i), predicted with the aid of the regression equation, is defined as:

$$b_o + b_1 x_i^{(1)} + b_2 x_i^{(2)} + \ldots\ldots + b_k x_i^{(k)}$$

The regression analysis program

In treating the data, as stated above, a weighted regression analysis program (WRAP:M.D. Fimple, Sandia Corporation, Sandia Base, Alberquerque, New Mexico) was used. The following details are reproduced from the authors description.

Features of WRAP

A. Since, in practice, a considerable number of regression problems are encountered in which the assumption of constant variance is not met, an option was included to do weighted regression analysis.

B. A feature of engineering experiments is that, in general, several "output" or "dependent" variables are measured, as well as many independent variables in a single pass. This results in some computing economies and gives these analyses in a more convenient form for the statistician and engineer. At the present time, on the 1604, WRAP will handle 80 independent variables and 25 dependent variables.

C. It is common to analyse some transformation of a variable, rather than the raw data. Most regression programs allow some transformations, but do not allow much flexibility in this respect. The Weighted Regression Analysis Program includes an interpretive system which allows the user almost complete flexibility in transforming, combining, moving, and coding the input data. The interpretive system is very simple and easy to use. Most of the instructions in the system are quite powerful, giving the desired results with a minimum of programming by the user.

Some special coding instructions are included to facilitate the analysis of qualitative data, together with a special instruction useful in coding the dependent variables for discriminant function analysis.

D. The method used by WRAP to pick the most significant subset of independent variables for each dependent variable is as follows:

1. The regression analysis is performed on the entire set of k independent variables.
2. For each variable in the analysis, the statistic

$$\frac{b_i^2}{C_{ii}}$$

is computed, where b_i is the regression coefficient giving the relationship between the i^{th} independent variable and the dependent variable. C_{ii} is the i^{th} diagonal element of $(X'X)^{-1}$. This statistic gives the reduction in the regression sum of squares when X_i is deleted from the analysis.

3. The minimum $\frac{b_i^2}{C_{ii}}$ is obtained.
4. This value is divided by the error mean square at that point, and this ratio has an F distribution.
5. This value of F is tested against either a value of F or a probability level included in the control card for the problem.
6. If it is determined that this minimum sum of squares is significant, the deletion process is discontinued. Otherwise, X_i is deleted, the inverse matrix is adjusted for the deletion, and a branch is taken back to step 2.

E. Since the method given above for selecting the optimum subset of variables is equivalent to partially reinverting the X'X matrix, it is essential to include a check on the accuracy of the inverse. It should be pointed out that all operations are carried out on the correlation matrix which has all elements between ± 1. The basic inversion routine used throws out any variables which would cause singularity. After the correlation matrix is inverted, the norm of

$$(I - RB_o)$$

is computed. I is the κ x k identity matrix, R is the correlation matrix, and B_o is the computed estimate of R^{-1}. The norm used is defined by

$$N(A) = (\Sigma\Sigma\, a_{ij}^2)^{1/2}$$

If this norm does not meet the requirements specified on the control card, the option is available to use Hotelling's method (Harold Hotelling, "Some New Methods in Matrix Calculation". Annals of Mathematical Statistics, Vol. 14, 1943, pp. 1-34) to obtain a better estimate of the inverse. This is an iterative technique, and the i^{th} estimate of the inverse is given by

$$B_i = B_{i-1}(2I - RB_{i-1})$$

If the norm mentioned above is less than 1.0, convergence to the true inverse is assured (in theory). Actually, the degree of convergence is restricted by the use of floatingpoint arithmetic.

F. The output from WRAP is the following (optional output is indicated by *):

1. A listing of some of the information on the control card.

*2. Heading information supplied by the user and read in and put on the output tape at execution.

*3. The sums of all variables, and the sums of squares and cross products.

*4. The means of all variables, and the sums of squares and cross products, all corrected for the mean values.

*5. All correlation coefficients.

*6. The inverse of correlation matrix and the inverse of X'X.

7. The regression analysis for each dependent variable, which gives all the following information at each step of the deletion process:
   a. Analysis of variance for total regression.
   b. Residual variance and standard error.
   c. Multiple correlation coefficient and its square.
   d. Each regression coefficient, its standard error, t ratio, F ratio, and the sum of squares due to each variable.
   e. The variable to be deleted during that step.

*8. Residual information for each observation:
   a. Observed y value.
   b. Predicted y value.
   c. Difference, a - b.
   d. The ratio, c/residual standard error.
   e. The weight assigned to the observation.
   f. The standard error of the individual observation based on $(X'X)^{-1}$ and the weight.
   g. The ratio, c/f.

*9. A listing of the data generated by the interpretive system and analysed.

CHAPTER IV

EFFECT OF PREOPERATIVE CONDITION ON MORTALITY WITHIN 30 DAYS AFTER OPERATION

This part of the investigation shows how multiple regression analysis was used to estimate the effect of various preoperative factors on mortality within 30 days after the operation. This analysis attempts to shed light on two groups of problems: the problems of prognosis or prediction, and the problems of coefficient estimation and interpretation.

A. THE MATERIAL AND THE VARIABLES STUDIED

All the 191 patients described in Ch. II were included in the study. The division into diagnosis and operation groups has been shown in Tables 2 and 3 (p. 92). The preoperative variables listed in Ch. III have been included in the analysis, as well as the peroperative factors of prime and type of anesthesia, since the choice between various primes and types of anesthesia is made preoperatively. The average and SE of the average of a number of preoperative factors for each operation group have been shown in Tables 4 and 5, where the "general degree of severity" consequently appears in broad outline. The mortality within 30 days after the operation has been chosen as dependent variable (y), because it is relevant and ascertainable without objection.

Observed mortality within 30 days after operation

Forty-nine patients out of the 191 died within 30 days of the operation, 10 of them within 24 hours (mortality group 1), 31 between 1 and 10 days (group 2) and 8 between 11 and 30 days (group 3). The distribution of the deaths over the various operation groups is shown in Table 6 A. The data concerning sex, age, diagnosis, preoperative status, operation performed, perfusion data, effect of repair, prime, type of oxygenator, possible complications and autopsy findings have been grouped together for each case. The object was to analyse the causes of death as a basis for the calculation of the predicted risk of death, and to investigate whether significant intravital changes were present at the time of the operation without being clinically recognized earlier. On the basis of this investigation of all the cases of death, a classification according to the various causes of death was attempted. The result is set out in Table 6 B.

General observations on Table 6 B

The 11 fatal cases resulting from sepsis all concerned patients with inserted prostheses (eight with Starr prostheses in the aorta, two cases of shunt with intracardiac patches and one with a Teflon graft in the aorta). Of these cases, eight had no antibiotic supplement in the oxygenator, while two had penicillin (10-20 million units) and one chloromycetin (2 g) in the priming volume.

Fourteen cases suffered acute renal failure. In all cases there were other simultaneous complications, such as sepsis, anoxia and/or low cardiac output for various periods.

Three patients certainly died and three probably died as a result of technical complications, while 10 most probably died as a result of coronary vascular anomalies or coronary sclerosis. In four of the latter cases the illness was not known before the operation, and in most cases there was probably poor coronary perfusion resulting from these changes, judging from the fact that heart infarctions

and damage from anoxia were common with these patients. Otherwise there were few important preoperative changes that were unknown.

In summary, it can be stated that practically all the fatal cases can be explained, but that only a few of them can be explained solely by the per- and postoperative complications. In all the other cases it is not out of the question that the preoperative state of the patient to some extent contributed to the appearance of fatal complications.

B. SIMPLE CORRELATION ANALYSIS BETWEEN MORTALITY AND PREOPERATIVE VARIABLES

It can be seen from the correlation coefficients between the relevant x-variable and y which preoperative factors in this material had the greatest correlation to the 30-day mortality. It is clear from the xy correlation coefficients of the 191 patients that greater age(*), acquired defect(*), greater heart volum(***), higher serum Na(*), reduced work-test(*) and the squares of age(**), heart volume(**) and work-test(*) show significant positive connection with mortality. There is a non-significant connection (correlation coefficient less than 0.1420(*)) between the following preoperative factors and the mortality. The mortality increases with an increasing number of diagnoses, a longer period of incapacity for work, in cases requiring preoperative treatment with both digitalis and diuretics ("preoperative insufficiency"), a low preoperative K^+ value, a high preoperative HCO_3^- value and the occurrence of "other ECG changes". A non-significant negative correlation obtains between primes containing Rheomacrodex + mannitol or mannitol only, and between operations using the disc oxygenator (instead of the bubble oxygenator) and the mortality.

Of the characteristics for the various groups of operations, the following proved to attain the highest correlations on simple analysis: final diastolic pressure in LV and PCV at rest in cases of operations on the aorta (a significantly more marked correlation with y than, for example, the aortic gradient or the degree of aortic insufficiency), preoperative systemic blood-flow in the cases of operations on the mitral valve, PCV at rest for shunt cases (except Fallot´s tetralogy) and preoperative hemoglobin in cases of Fallot´s tetralogy. For group III (combined operations on the aorta and the mitral ostia), which comprised only 12 cases, the risk of mortality increased, in this order: greater degree of insufficiency(*), in the mitral valve greater systemic blood-flow, higher end-diastolic pressure in LV, higher PCV at rest, greater aortic gradient and greater degree of aortic insufficiency.

C. MULTIPLE REGRESSION ANALYSIS

If it is desired to study how a single factor, such as a patient´s preoperative heart-volume or age affects the outcome of a surgical intervention, a simple correlation analysis (study of the effect of an isolated factor without considering other factors) is inadequate, as the possible effect of other, possibly more significant factors correlated to the factor studied is not taken into account.

Thus, if the problem is to find the true prognostic value of each factor and to determine which factors have the greatest importance, a regression analysis involving multiple factors should be used. Such analysis results in an isolation of the influence of each factor. Thus, for example, one may calculate the 30-day postoperative mortality-rate difference between patients with different heart volumes which would exist if these patients were similar as to distribution of sex, age, type of heart lesion, etc. (the ceteris paribus principle). In the analysis all such factors must be included as independent variables (regressors). The dependent variable (regressand) is the 30-day postoperative mortality. The number of independent

variables should be as great as possible to make the patients similar in still more respects. The regression coefficients computed represent an estimate of the influence of the respective factors on the mortality rate. However, when interpreting the results of the regression analysis, the possible causal relations between different independent variables must be considered. In a regression analysis of linear model the regression equation is: $y = a + bx + cz$. The coefficients b and c for two independent variables (x and z) are calculated according to the principle of least squares. It must be emphasized that this type of model, and the extensions thereof used in this study (see Ch. III, B), is approximative. Thus, squares of variables and/or combinations of factors may have a particularly great prognostic influence. This problem may be solved by introducing interaction variables into the regression analysis or diverting from the linear model by introducing squares of the variables. Another disadvantage of the linear model is that some factor combination may give mortality risks less than 0 or greater than 100 per cent i.e. absurd predicted values.*

This problem may be solved by exchanging the linear model for much more complicated equations excluding the possibility of absurd y values. In the present study all the above mentioned diversions (except the last) from the simple linear model have been tested or utilized.

D. APPLICATION OF MULTIPLE REGRESSION ANALYSIS TO THE MATERIAL

A series of regression analyses were carried out on the above principles at the Uppsala Data-Processing Centre. The computer used was a Control Data Corporation 3600. The programme was a weighted regression analysis (WRAP; see page 26), permitting simultaneous analysis of 80 regressors (x) and 25 dependent variables (y). There are a large number of independent variables to begin with, but these are deleted one by one at a predetermined level of probability (p-level or reduction criterion). The analysis stops when all remaining regressors have t-values with probabilities equal to or greater than that level. All regressors which are not deleted have a P value (significance level) equal to 1- (the level of probability used). If, for example, the level of probability in an analysis is fixed at 0.95, then all variables are deleted except those which have a P value < 0.05 (*). (test of the null hypothesis: regression coefficient = 0).

1. Preliminary analyses

The final analysis must be performed in a series of steps, because of the large number of regressors. To investigate the most convenient form for this, a series of preliminary analyses were carried out, in which the change of coefficient was studied (a) within the same analysis, (b) with different values of probability level, (c) in comparisons between different materials and (d) with the re-introduction of deleted regressors. An attempt was also made (e) to reduce the total of "absurd" predicted values by assigning certain individuals greater weight in the analysis. In assessing the suitability of different forms of analysis, account was also taken of changes in residual variance and of the total correlation coefficient (R) which can be said to show to what extent the connection between observed and predicted values can be explained by the regressors included in the analysis. In Fig. 1, the course of the analysis is presented schematically.

*After each regression analysis, a statement of the predicted risk of mortality for each patient is obtained by data-processing. In this connection the product between the regression coefficients and acutal value of the remaining regressors for each patient is obtained. The sum of the products is obtained and to this is added the constant, from which the predicted value is obtained. The regressors with the greatest correlation to y after reduced analysis will thus greatly affect the prediction for each patient.

(a) Changes of coefficient within the same analysis. In one analysis of 74 regressors (linear, combined and squared variables) at a p-level of 0.95 (*) there remained 15 regressors after reduced regression (Fig. 1, step 1 c), all regression coefficients differing from 0 by a risk of error $\leq$ 0.05. Table 7 shows the changes in the coefficient values, the SE and the significance level during the analysis. The comparison reveals that only a few regressors have attained a significant level in the non-reduced regression. One notes, too, that the strengthening of the connection between the x variable in question and the mortality (y) which is apparent during reduced regression is mainly due to a reduction of the SE of the x variable. The residual standard deviation (RSD), on the other hand, underwent only insignificant changes.

(b) Influence of different levels of probability. The same analysis of the effect on mortality within 30 days of the operation of 74 preoperative variables as shown in the preceding section was also used (Fig. 1, step 1 a-c) in a comparison between the effect of different levels of probability on the number of deleted variables. At a probability level of 0.05 no variable was deleted; at 0.70 38 were deleted and at 0.95 59 were deleted. In this comparison it was also found that the residual variance was lowest at the probability level of 0.70, as is seen in Table 8.

(c) Influence of differences in the composition of the material. As stated above, 10 of the 191 patients died within 24 hours of the operation. Data concerning some peroperative factors were lacking in these cases, so that a uniform substitution was not possible. It is therefore possible to study the effect on the mortality of both pre- and peroperative factors in a material of only 181 patients. To get an idea of the effect of the loss of these 10 patients on the coefficient values and significance levels, the following comparisons were made (Fig. 1, step 1 b and 2). Seventy-four preoperative variables were analysed at a p-level of 0.70 both for 191 and for 181 patients. After the analysis 36 regressors remained for 191 patients and 38 for 181. Twenty-four were common to both materials. Of these, 20 attained a significance level of (*) in one or the other, but only six had the same significance level. Of the remaining 12 non-common regressors for 191 patients, two attained a significance level of (*) . Of the 14 of 181 patients, the corresponding number was three. As such striking differences existed with regard to the choice of remaining regressors between the two materials, a closer investigation was considered necessary. This was performed as follows (Fig. 1, steps 3 (b) and 4). The remaining regressors from 191 patients were included in an analysis for 181 at a p-level of 0.00. The coefficient values obtained were thus directly comparable. A strikingly good agreement was obtained in the coefficient values, SE and significance level. In the analysis of 191 patients R^2 was 0.507 and in the analysis of 181 patients, 0.502 (the corresponding RSD values were 0.331 and 0.315).

In this comparison (Fig. 1, steps 3 (b) and 4) 37 absurd predictions were obtained with 191 patients, as against 47 for 181 patients (19 % compared with 26 %).

(d) Influence of the re-insertion of deleted variables. In order to ascertain whether the prediction could be improved if a number of preoperative factors used clinically in connection with the prognosis but deleted in the analysis were re-introduced, a new analysis was carried out. In this were included, besides the 26 factors (Fig. 1, step 3), sex, age, congenital or acquired defect, all operation groups, period of symptoms before operation (in years), medication with digitalis and/or diuretics (called here "preoperative insufficiency") and combinations between all the operation groups and their catheterization data and ECG status (Fig. 1, step 6 a). The result of this analysis showed that the 26 remaining variables largely re-

tained both their coefficient values and their degree of significance, that none of the re-introduced variables attained significance, and that most of these had a very high SE. Moreover, the number of negative absurd predicted values increased to 45 less than 0 (from 37). The total prediction was 49, that is, 49 fatalities = the observed number, but if the absurd predicted values were counted as 0, the total number of predicted deaths became 54, that is, five more than the right number. Thus the re-introduction of the variables earlier deleted involved no improvement from the point of view of prediction, whereas the total number of predicted deaths calculated according to the 26 remaining regressors only was 53, that is, four more than the observed number of deaths.

(e) Absurd predicted values and influence of differentiated individual weights. As has already been mentioned, absurd predictions occur, that is, a number of patients have predicted death risks that are under 0 % or over 100 %. In the previously described analysis of 74 preoperative variables at three different levels of probability (Fig. 1, step 1 a-c) it appeared from an examination of the predicted death risks, that an increase of probability level to 0.95 involved a shift of these risks towards the average. The number of predicted death risks under 0 % for a p-level of 0.05 was 38, for 0.70, 40 and for 0.95 28. If the absurd predicted values are added together, this difference between the last group and either of the others is statistically highly significant (***). A higher p-level (increased reduction criterion) is thus a way of reducing the number of absurd predicted values - at least in this material.

Another way of reducing the number of absurd predictions is to allot the patients who have risks less than 0 or over 100 % extra weighting compared with the others (Fig. 1, steps 5 and 6 b). The weighting is arranged so that the desired number of x-variables is analysed at weight 1 for all patients. The predicted values for the patients are examined and the patients who have received absurd values are allocated a higher weighting than the others and a new analysis is then carried out. In the present case, in which weighting of 4 and 9 were tried, the number of absurd predicted values could certainly be reduced by this procedure (from 37 to 22 at weighting 9) but it simultaneously appeared that in part quite different patients now received values under 0 or over 100 %. Thus, in attempting to eliminate absurd predictions in this way, a programme that repeats the weighting process until the predictions for all patients fall between y-values of 0 and 1 would be needed.

(f) Results of preliminary investigations: Summary. The preliminary regression analyses intended to form the basis for a final form of analysis have been described above under subsections (a)-(e). The following results were obtained.

The highest probability level tested (0.95), when all remaining regressors had a significance at least (*), proved to have the following advantages and disadvantages, both within the same analysis and in comparisons between different analyses. The advantages were that the number of remaining regressors was less, the coefficients of the remaining regressors attained a higher significance level (mainly through reduction of the SE) and the number of absurd predicted values was significantly reduced. The disadvantages were that regressors with relatively marked but non-significant connection with y are excluded from further analysis and the SE for the remaining regressors are probably reduced much more than is justified.

Comparisons between different selections of patients which are desirable because patients who died within 24 hours of the operation had no peroperative values, have shown that R^2 is better at 191 than at 181, that regression coefficients and

significance levels are roughly equivalent, and that the number of absurd predictions is less at 191.

Comparisons between final regressors obtained in reduced regressions and these plus the re-introduced preoperative factors show that no improvement is obtained, either of explanatory values or of prediction, as a result of the re-introduction of factors, earlier deleted.

2. Final programme of analysis

As a result of the preliminary analyses it was decided that the final analysis of the effect of the preoperative factors on mortality within 30 days of the operation should be carried out on all 191 patients at a probability level of 0.95.

At the first stage (step 1) 80 preoperative regressors were analysed, of which 45 were linear variables, 25 interaction regressors (between operation groups and their preoperative catheterization data), and 10 variables in quadratic form at a p-level of 0.95. At the second stage (step 2) the remaining regressors from the first stage (25) were analysed, together with 55 combinations of these regressors and all the operation groups (except group VII, in order to avoid singularity) and the squares of those remaining variables not previously squared, at a p-level of 0.95. Stage 2 included a further two analyses, at p-levels of 0.990 and 0.999.

After the two final regression analyses (steps 1 and 2) 31 regressors remained. These are shown in Table 9, together with their coefficients, SEs and significance levels in unreduced and reduced regression. The coefficient value in the preceding reduced regression of the 10 remaining regressors from stage 1 is also given. Table 10 shows the connection between the remaining 31 regressors both reciprocally and between each separate variable and the mortality (the xx and xy correlations). From considerations of space, only the number of the variable is given in the table, since the explanation is shown in Table 9, where the corresponding number is to be found. For the correlation coefficients (r) (191 patients) the following significance levels apply: $0.1420 \leq |r| \leq 0.1859$ = *, $0.1860 \leq |r| \leq 0.2362$ = ** and $|r| > 0.2362$ = ***.

For the sake of clarity, slight correlations (like $|r| < 0.1000$) have been shown as $\pm \phi$, while somewhat more marked but non-significant coefficients are expressed as $\pm 0.1000 \leq |r| \leq 0.1419$.

In the two steps of the final regression analysis the original factors were eliminated one by one, so that a combination of 31 factors finally remained. This combination thus proved to give the best adaptation to the actual values (0 or 1) for the patients included in the material. Since these 31 factors were chosen from about 150 single, combined or squared preoperative factors and the p-level (reduction criterion) was adjusted so that the remaining factors attained at least (*) significance ($p \leq 0.05$), there is a chance that 5 % of the 150 original variables remained, in spite of the fact that they had no real correlation with y. Among the 31 remaining factors, 7.5 thus might have remained as a result of chance and not because they had a real correlation with y. To remove these, two further regression analyses were carried out in accordance with step 2 of the final analysis, but the p-level was set at 0.990 and 0.999. Thus in the first analysis 1.5 regressors and in the second 0.15 regressors may remain through chance. At a p-level of 0.995, 11 regressors remained, namely, $(\text{heart-volume})^2$ (with the coefficient 2.56×10^{-7}), which for all patients meant a risk of death of 6 % at a heart volume of 500 ml/m^2 and of 26 % at 1000 ml/m^2 (hence an increase of 20 %) and incapacity for work in years, though with different significances for each operation group. In group I an increase of incapacity for work by one year involved an increased risk of 7 %,

for groups II and IV 0 %, for group II -22 %, for group V 0 % and for group VI 3 %. Moreover for operation group I, two diagnoses instead of one meant an increased risk of 22 %, while the end-diastolic pressure in LV involved an increased risk as follows: 0 mmHg 0 %; 10 mmHg $10^2 \cdot 0.000287$ or 3 %; 20 mmHg 11 %; 30 mmHg 26 % and 40 mmHg 46 %. The risk was reduced with an increasing degree of insufficiency in operation group I. In group III preoperative systemic flow was not deleted; an increase of 1 l/min meant that the risk increased by 1 %.

In the second analysis (p-level 0.999) only 7 variables remained, namely (heart volume)^2 and incapacity for work in years, partly for all patients, and partly with an additional coefficient for each operation group. In this analysis heart volume of 500 ml meant a risk of 0 %, while a heart volume of 1000 ml/m^2 meant a risk of 22 %. The significance of an increase in incapacity for work by 1 year was +8 % for group I; -5 % for groups II and IV; -8 % for group III; 0 % for group V and +2 % for group VI. In the case of "other operation" (group VII) the risk resulting from increased heart volume was the same as for the other groups, but it increased by 38 % for 1 year´s incapacity for work. In these two analyses, and especially the latter, steps were accordingly taken to ensure that no regressor was included without having a positive correlation with the mortality. R^2, which in the analysis at a p-level of 0.950 when 31 regressors remained, was 0.569 (residual variance 0.0988) fell at a p-level of 0.990 to 0.307 (residual variance 0.141), and to 0.181 (residual variance 0.163) at a p-level of 0.999. The explanatory value for the correlation between predicted and observed mortality among the remaining regressors thus fell rapidly with an increase in the reduction criterion. As a matter of fact the maximum explanatory value (lowest residual variance) of the remaining regressors is at a p-level of 0.80. When 51 regressors remained, R^2 was 0.568 and the residual variance 0.0895. This weakening of the correlation also emerged in the predicted values for risk of death. In the latter analysis, only 9 of the 49 cases of death received more than a 60 % risk of death, and in the former, 16 out of 49. If we compare the prediction at p = 0.95 and p = 0.99, the following differences for the operation groups are obtained.

	p-level 0.95 Pred.rate		p-level 0.99 Pred.rate		No of deaths
	<40 %	>60 %	< 40 %	>60 %	
Operation group I	6 pat.	14 pat.	12 pat.	5 pat.	24
II + IV	1 "	2 "	3 "	2 "	5
III	0 "	5 "	0 "	3 "	5
V	0 "	0 "	3 "	0 "	3
VI	1 "	3 "	3 "	1 "	4
VII	1 "	7 "	1 "	5 "	8

This table shows that in the material studied the mortality within 30 days of the operation can be predicted for rather more than half of the cases in which the aortic valves were operated on and for 85 % of the others by analyzing (at a p-level of 0.95) the patients´ preoperative status. An even greater proportion of correct predictions could probably have been made if a p-level of 0.80 had been used.

3. Interpretation of coefficients

The coefficients for 31 regressors remaining in the final analysis at a p-level of 0.95 are shown in Table 9. These would seem to be primarily an expression of the effect of individual regressors per se, that is, the effect that would result

if all factors other than that studied were fixed (ceteris paribus).

However, certain regressors are probably to be treated as indicative of other factors that are more essential, but have either not been included or have been deleted from the analysis. Thus, for example, an extended period of incapacity for work and/or lower preoperative systemic blood flow involves a reduced risk of death for patients who had combined operation on the aortic and mitral valves. This is due to the fact that this group of patients includes 7 cases with combined mitral stenosis and aortic insufficiency, in which the intervention involved the insertion of a prosthesis in the aortic ostium and transventricular instrumental dilatation of the mitral valve. One of these patients died postoperatively. The average incapacity for work was 1.5 years and the preoperative blood-flow was low. In 5 cases prostheses were inserted in both ostia because of AI + MI. Four of these patients died. The incapacity for work was only 2 months on average, and the preoperative blood-flow on the average was considerably higher than among the former group. The apparently absurd effect of these regressors is thus a reality in the material analysed here, and is due to the composition of operation group III and to the extended period of illness with the MS and AI combination.

On the other hand, some regression coefficients may have attained significant divergence from 0 as a result of chance. There is a considerable risk of this, because of the reduction method used to diminish the number of original regressors. Chance may also have been decisive as regards whether an individual survived or not, especially as only preoperative variables were analysed, and it can be presumed that per- and postoperative complications also contributed to the mortality. The chance effect may be of decisive importance with respect to the size of the material. The absolute medical significance of the remaining regressors may thus be uncertain but an interpretation of the coefficients may nevertheless interest as it is thereby possible to build up and test a scheme with the help of which the operation risk for patients other than those included in the material can be predicted.

The interpretation of the coefficients proceeds as follows:

Significance of number of diagnoses per patient

	No. of diagnoses		
	1	2	3
For all operation groups	-1.107	-1.032	+0.225

These figures are obtained by including 1, 2 and 3 diagnoses in both "number of diagnoses" and ("number of diagnoses")^2 (regressors nos. 3 and 22 respectively) in Table 9. A patient with coronary sclerosis, for example, in addition to AI + AS, thus received an expected increase in the predicted value by -1.032 - (-1.107) = +0.075. Since y = 0 signifies survival and y = 1 death within 30 days of the operation, this value can be converted directly to the percentage increased risk of death, viz. 7.5 %. Only 1 patient (operation on aortic valves) belonged to three diagnosis groups, and the coefficient in this case was adjusted, so that his risk of death was exactly 100 %, whence the great increase in risk in this analysis between two and three diagnoses. It may also be pointed out that operation group III always had two diagnoses and groups VI and VII always only one diagnosis.

Height-weight. Weight in relation to height was significant for all the patients (the height minus weight difference was obtained).

This difference is:

85:	+6.76	
90:	+6.87	
95:	+6.93	
100:	+7.00	$(100 \times 0.136 + 100^2 \times (-0.000664))$
105:	+6.96	
110:	+6.93	
115:	+6.86	

The average height-minus-weight is 102.5 for this material. The table above, shows that the risk of death was reduced when the patient was either over- or underweight. The risk figure holds on the assumption that other factors are constant (ceteribus paribus) and this was clearly not the case. Height-weight served as a damping factor on others stronger in the outer areas or was a symptomatic factor.

Incapacity for work 1 year involved an increased risk of death of:

Operation group I	10 x(0.0384 - 0.0323) =	+0.061	or 6 %
II + IV		+0.062	" 6 %
III		-0.197	" -20 %
V		+0.005	" 1 %
VI		+0.014	" 1 %
VII		+0.384	" 38 %

For operation group III (combined aortic and mitral operation) incapacity for work of 1 year before the operation thus meant that the patient had a (20 %) greater chance of survival (see the above explanation).

Preoperative heart volume

		Operation group no.					
		I	II+IV	III	V	VI	VII
Risk of death	300 ml/m^2	+0.043	+0.026	+0.100	+0.003	-0.031	+0.100
at heart volume:	400 "	+0.077	+0.047	+0.177	+0.005	-0.053	+0.177
	500 "	+0.120	+0.073	+0.277	+0.009	-0.083	+0.277
	600 "	+0.172	+0.105	+0.399	+0.012	-0.120	+0.399
	700 "	+0.235	+0.144	+0.542	+0.017	-0.163	+0.542
	800 "	+0.307	+0.188	+0.708	+0.022	-0.212	+0.708
	900 "	+0.388	+0.237	+0.897	+0.028	-0.269	+0.897
	1000 "	+0.479	+0.293	+1.107	+0.034	-0.332	+1.107
	1100 "	+0.580	+0.355	+1.339	+0.041	-0.402	+1.339
	1200 "	+0.690	+0.422	+1.594	+0.049	-0.478	+1.594
	1500 "	+1.078	+0.659		+0.077		
	2000 "		+1.172		+0.136		
	2500 "				+0.213		

These values are obtained by combining in each operation group the coefficients for $(\text{heart volume})^2$ with that applying to all groups (no. 23, Table 9). For operation group I, the calculation was as follows: 0.000 001 107 - 0.000 000 628 = 0.000 000479. For a relative heart volume of 300 ml a value of 300^2. 0.000 000 479 = 0.04311 is obtained. Thus for operation group I (aorta operations) an increase of the heart volume from 500 to 1000 ml/m^2 meant an increased mortality risk of 0.479 - 0.120 = 0.359 (or 36 %). As is evident, the increase of heart volume had the greatest significance in operation group III (combined aortic and mitral operation) and group VII (other operations). In mitral operations and especially cases of shunt (apart from Fallot's tetralogy) the increase of heart volume had considerably smaller signifi-

cance. For Fallot´s tetralogy, it is evident that with increasing heart volume the risk was reduced. This could mean either that the surgical intervention is technically simpler or that a greater total heart volume means a larger left ventricle, better suited to take over the work when the shunt is terminated.

HCO_3^- in serum. The increase of the preoperative HCO_3^- value by 1 mE/l involved an increased risk of 0.050 or 5 % for all groups, except group V, in which the risk was instead reduced by -0.0891 + 0.050 = -0.0388 or -4 %. The marked and unexpected effect of this regressor may have been due to one of the following circumstances: the regressor was "lucky" and was not eliminated in the regression analysis; it is a "sign" or (representative) of a factor either not included or eliminated from the analyses; the significance of the regressor is genuine. As is apparent from Table 10, there were significant, positive correlations for the number of diagnoses, priming volume R + M, degree of aortic insufficiency, congenital or acquired defect and heart volume in operation group I, together with incapacity for work in operation group III. Negative correlations existed mainly in operation groups V and VI. Hence it is likely that this factor replaced the operation groups that were themselves eliminated from the analyses and that it partly acted as a levelling factor for inequalities within individual operation groups. A further possibility exists, namely, that this reflects a time relationship. The regressor was correlated with the additions of Rheomacrodex and mannitol in the priming volume, and this combination was used only during the last part of the investigation.

Prime containing both Rheomacrodex and mannitol. If this combination was added to the priming volume, the risk was reduced by 0.178 or 18 % compared with the other primes used. However, there is a significant positive correlation with HCO_3 the coefficient of which is positive. This reduced risk to the patients with this prime is consequently counteracted by the fact that these patients, more than others, incur increased risk of death from the HCO_3 factor, which here has an equalising effect within the material.

Besides the regressors reported, the following facts held good for the separate operation groups.

Operation group I (aortic valve operations)

Congenital or acquired defect: An operation on an acquired aorta defect involved + 0.349 or 35 % greater risk than an operation on a congenital defect.

End-diastolic pressure in left ventricle

				Risk of death
End-diastolic pressure, LV:	1 mmHg	: 1^2 . 0.00251	=	0 %
	5 "	5^2 "	=	1 %
	10 "	10^2 "	=	3 %
	15 "	15^2 "	=	6 %
	20 "	20^2 "	=	10 %
	25 "	25^2 "	=	16 %
	30 "	30^2 "	=	23 %
	35 "	35^2 "	=	31 %
	40 "	40^2 "	=	40 %

Other factors being equal, an increase of the end-diastolic pressure in LV from 0 to 40 mmHg meant an increased risk of 40 %.

Degree of aortic insufficiency. This grading was obtained by X-ray methods, according to the specification in Ch. III. It may have values from 0 to 4. If the respective values are inserted in No. 27, Table 9. the following result is obtained.

			Risk of death
Degree of aortic insufficiency	0		0 %
	1: 1^2	. 0.0391	-4 %
	2: 2^2	"	-16 %
	3: 3^2	"	-35 %
	4: 4^2	"	-63 %

An apparently paradoxical reduction in the risk of death occurs with an increasing degree of insufficiency. The explanation lies in the composition of operation group I, which includes both congenital and acquired aortic stenosis as well as aortic insufficiency. The mortality was very diverse for these groups and these differences are taken up by the regression coefficients.

	Relative risk of death	
	Aortic stenosis	Aortic insufficiency (degree 4)
Congenital	0 %	-63 %
Acquired	35 %	-28 %

It is clear from this that cases of acquired aorta stenosis ran a 35 % greater risk of death than congenital, and a 63 % greater risk than pure insufficiency. Congenital insufficiency in its turn involved a low death-risk. However, the material contained only 4 such cases (aortic insufficiency of degree 4 combined with VSD) and these, of course, belonged to more than one diagnosis group and therefore had an 8 % increase in the risk of death. The negative coefficient for the "degree of aortic insufficiency" regressor, is consequently in itself paradoxical, but functions in the actual analysis as a levelling factor between the various groups of which operation group I is composed.

For operation groups II and IV (mitral operations) the following factors also held good:

				Risk
PCV at rest	1 mmHg:	1^2	. -0.00145	0 %
	40 " :	40^2	"	-232.0 %
Systolic PA at rest	10 " :	10^2	0.000348	+3.5 %
	100 " :	100^2	"	348.0 %

As is evident from these two calculations, it was the combination of PCV and systolic PA that characterised the differences in the death-risk between the mitral operation patients, indicating the relationships that existed among the 28 patients included in the material.

For operation group III (combined aortic and mitral operations)

Blood-flow at rest: an increase of 1 litre in the preoperative blood-flow at rest increased the risk of death by 0.243, or + 24 % (see previous explanation).

Gradient aorta and (Gradient aorta)^2

With coefficient included

Gradient mmHg	Linear variable		Square		Total
10	10 . 0.0845 =	+0.845	10^2 . 0.00203 =	-0.203	+0.642
20	" =	+1.690	20^2 " =	-0.812	+0.878
30	" =	+2.535	30^2 " =	-1.827	+0.708
40	" =	+3.380	40^2 " =	-3.248	+0.132
50	" =	+4.225	50^2 " =	-5.075	-0.850
60	" =	+5.070	60^2 " =	-7.308	-2.238
100	" =	+8.450	100^2 " =	-20.300	-11.850
150	" =	+12.675	150^2 " =	-45.678	-33.003

Cl in serum. An increase of 10 mE reduces the risk by 10 . 0.0129 or 13 %.

Operation group III contains only 12 cases and therefore all the factors reported here were given positive or negative coefficients such that the adaptation to the mortality would be as favourable as possible for the patients in the group. The coefficients and signs reflect background factors rather than their own real significance.

Operation group V (shunt cases, except Fallot´s tetralogy)

Cl^- in serum. An increase of 10 mE/1 increases the risk by 10 . 0.0206 or + 21 %.

("Other ECG changes"). According to the definition in Ch. III, this factor was recorded as grade 1, 2 or 3. Grade 1 involved 1^2 . 0.0492 or + 5 %, grade 2 involved 2^2 . 0.0492 or + 20 %, and grade 3 involved 3^2 . 0.0492 or + 44 % risk.

In this group only three fatal cases occurred among 23 patients (2 of them with AV commune, 1 with VSD) and therefore the significance of this factor partly reflects the distribution within this special material, with uncertain general significance.

Operation group VI (Fallot´s tetralogy)

Gradient RV-PA. An increase of 10 mmHg means risk reduced by 10 . -0.00608 or -6 %.

Preoperative hemoglobin. An increase of 1 g% increases the risk by 1 . 0.0762 or 8 %. Of these factors, the latter is probably "genuine", while the former moderates the significance of high hemoglobin values and acts as an equalizing factor between the 18 patients in the group.

4. Prediction of risk of death

The 31 regressors obtained as a result of the final analyses give the following distribution of predicted values:

Hence 95 % of the living cases fall within ± 40 % of 0 % and 63 % of the dead within ± 40 % of 100 %. There are 16 patients between 41 % and 60 % predicted death-risk, of whom 9 died. Nine of the 49 dead fell below 40 %, that is, the risk of false prediction is 9:144, or 6.3 %. The final analysis gives a value for R^2 of 0.569, showing that the remaining combination of 31 regressors can to a great extent explain the incidence of deaths in the material.

However, the result is impaired by the patients who died despite low predicted values. An investigation of the causes of death among these cases may therefore be justified. As is evident from the comparison, 12 patients with predicted values below 50 % died.

Predicted value 7 %. ♂ aged 49. AI + AS. Starr. Died after 3 days with extensive anoxic brain damage and acute renal failure. The post-mortem showed anomalies in both coronary arteries (separate ostia on the left, pronounced hypoplasy of the right, together with slight coronary sclerosis), both findings were undetected before the operation.

Predicted value 16 %. ♀ aged 31. Fallot's tetralogy. Total correction. Died after 5 days from heart failure. Poor result of repair (systolic pressure in RV fell from 135 to 90 mmHg).

Predicted value 17 %. ♀ aged 49. MI + MS. Starr. Bubble R + M. Died of subdural hematoma + left ventricular failure on table.

Predicted value 23 %. ♂ aged 42. AI. Disc. B + R. Died as a result of sepsis.

Predicted value 23 %. ♂ aged 18. AI + VSD. Starr and Teflon prosthesis. Disc B + R + M. Anomaly in left coronary artery, unknown prior to operation. Poor right-sided coronary perfusion during operation. Death after 2 days, as a result of acute renal failure, amongst other things.

Predicted value 25 %. ♂ aged 47. AI. Starr. Disc B + M. Died as a result of sepsis.

Predicted value 31 %. ♀ aged 57. Aneurism of aorta ascendens (lues). Disc B + R. Died during operation while aortic wall did not hold sutures.

Predicted value 33 %. ♂ aged 53. AI + AS. Starr. Bubble. R + M. Died after 2 days' unconsciousness with extensive anoxic brain damage and fresh ventricle septum necroses. Frequent postoperative ventricular fibrillations (38 electric shocks applied).

Predicted value 38 %. ♂ aged 41. AI + AS. Starr. Disc. Blood only. Frequent irreversible ventricular fibrillations lasting until death after 12 hours. Cause unknown.

Predicted value 41 %. ♂ aged 47. MI + Starr. Disc B + R. Technical complications (aorta iliaca ext. split at a.sc. plaque). Circulation stoppage for 12 min at 31° C. Extensive anoxic brain damage, haemorrhagia cerebelli.

Predicted value 42 %. ♀ aged 46. AV-commune. Teflon prosthesis. Disc B + R. Total block (pacemaker). Died after 7 days as a result of sepsis.

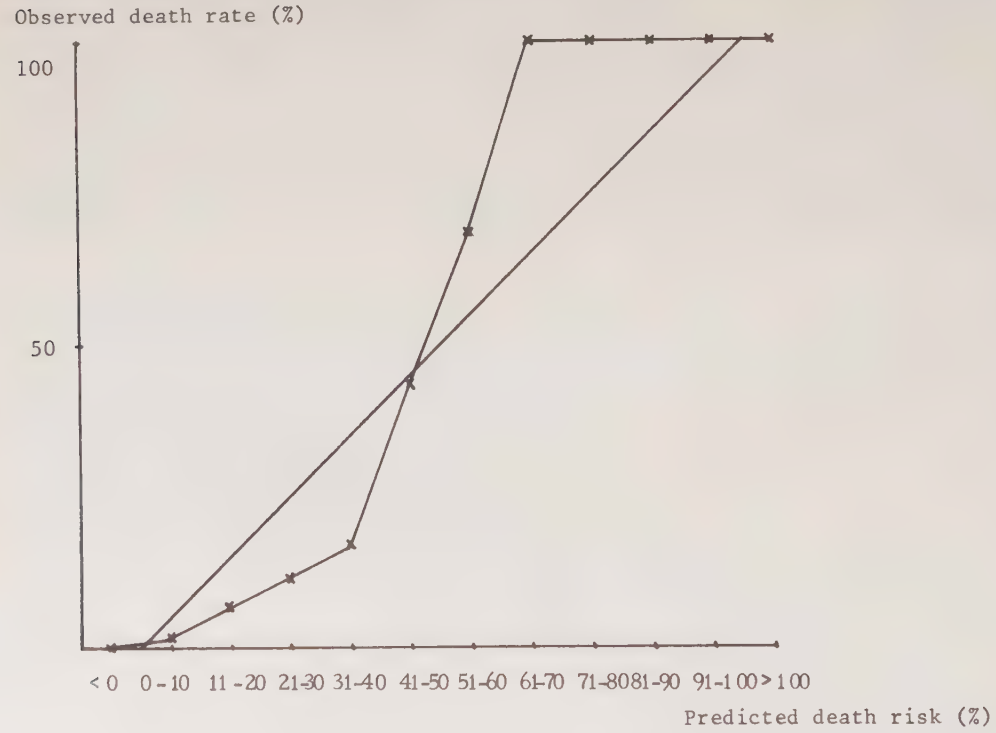
Predicted value 46 %. ♀ aged 40. AI. Starr. Disc B + M. Frequent ventricular fibrillations and varying rhythm postoperatively, lasting until death after 2 days. Low blood-flow and poor right-sided coronary perfusion under ECC. Edema and hemorrhage in cerebrum on autopsy.

Thus, of the 12 patients with predicted values under 50 %, 4 died as a result of anatomical changes that were unknown before the operation. Three died of sepsis, 3 from brain damage received during the operation and from unknown cause 12 hours

after the operation, and 1 from the deleterious effect of inadequate surgical repair, with progressive heart failure.

In these cases the cause of death could thus not be traced back to the preoperative factors recorded and used in the analysis. The comparison shows, however, that the prediction can be improved if, for example, the coronary arteris are carefully mapped preoperatively and if sepsis can be prevented. The operation and the extracorporeal circulation naturally involve a risk that cannot at present be predicted preoperatively for the individual patient.

By way of summary, it can be stated that the 31 regressors obtained in the final analysis provide a good prediction of the mortality risks for the patients included in the material. The prediction is good to the extent that the individual values do not represent the risk figure but show a certain adaptation to the ideal result of prediction, that is, when all the surviving patients obtain the value 0 and all the dead 100 %. This is shown by the figure below, where the relationship between the number of living and dead patients within each group of predicted values shows consistent deviations at the beginning and the end of the period instead of following the line that indicates the percentage risk within each prediction group.



5. Forecast index

The foregoing section described how the death risk can be predicted with the aid of the results of the regression analyses. An example of this procedure is given in Table 11, where, by inserting the real values for a case from mortality group 1 in the regression expression which included 26 regressors (from step 3 b) of the preparating analysis, a predicted death risk of 55 % was obtained. The final 31 regressors described above show that in this material quite good predictions of the operation risk can be obtained even at the preoperative stage. Predictions of the risks or prognoses can be given in a simpler, though somewhat less reliable way, in the form of a forecast index. This can be drawn up in several ways. In this case the values from the section entitled "coefficient interpretation" are simply converted into a points system, in which the number of points can be directly converted into the percentage risk of death. The general coefficient (or constant a, in the equation $y = a + bx + cz \ldots$) is changed in the conversion to a points system, by putting the middle group in certain variables equal to 0 and is corrected by reducing the original general coefficient. All patients included in the material were given predictions according to the forecast index, and the general coefficient for each operation group was adjusted, so that the sum of the forecast numbers agreed with the sum of the prediction numbers, according to the regression analysis.

This forecast index is shown in Table 12. Predictions were made for all the patients in the material from this table. However, for good agreement with predictions using coefficients directly, as exemplified in Table 11, one must interpolate or possibly extrapolate certain values, where the step within the classes in the forecast index would otherwise be too great. For example, incapacity for work for operation group I of 0.5 years would equal + 3 points and 1.0 years would equal + 6 points. If the classes were used directly, the variation in the prediction in single cases becomes more than ± 10 %.

This forecast index is so dependent on the material analysed that several regressors were given absurd values, in order to make the adaptation to y as satisfactory as possible. With this forecast index one can predict the death risk for the patients in the material, with a small percentage of error, while the result is much inferior when other patients´ death risks are predicted on the bases of their preoperative status. Of 46 patients operated on during 1962 before the commencement of the investigation or during 1965 after its completion, 21 of the 28 survivors and 7 of the 18 who died within 30 days had predicted values under 40 % and 1/28 and 7/18 respectively values over 60 %. The risk of error in a predicted value under 40 % is consequently 25 % and in a predicted value over 60 % it is 12.5 %. Although there is a certain limited possibility of predicting the risk, the system nevertheless has considerable weaknesses, for other reasons, because of the large jumps in the risk points caused by even small variations in certain variables. There are specially large weaknesses for operation groups III and VII, where the forecast index is based on only 12 and 14 patients respectively. These groups also show the greatest variations in predictions for patients not included in the material.

Attempts to produce a more generally applicable forecast index were made in several different ways.

(a) As has been mentioned, an attempt was made to pursue the analysis until only relevant and certainly significant regressors remained. In this case the regressors and regression coefficients obtained are easy to analyse, but have a relatively slight correlation with y (low R^2).

As appeared from the comparisons between the predicted values obtained in final analyses at p-levels of 0.95 and 0.99, the adaptation is considerably improved if several regressors are included in the prediction. In the latter analysis (p-level of 0.99) five regressors remained for operation group I. From these it can be concluded that a patient who has an aorta defect, a heart volume of 800-1000 ml/m^2, an end-diastolic pressure in the LV of 30-40 mmHg and has been incapacitated for work for 1-3 years has about a 10 % chance of survival, if predominant aortic stenosis is present, about a 50 % chance if there is pure insufficiency and very little chance at all if aortic stenosis and, for instance, coronary sclerosis or coronary artery anomaly are simultaneously present.

(b) Another attempt at generalization was made in the following way. On the basis of original xy correlations and remaining regressors in the final analysis, a number of regressors for each operation group was chosen, and analysed at a p-level of 0.00, (none were deleted). The regressors were as follows.

Operation group I (aortic valve operations). Congenital or acquired defect, more than one diagnosis, time of incapacity for work, "preoperative insufficiency" and squares of age, heart volume, work test and end-diastolic pressure in LV. In addition, the degree of aortic insufficiency was replaced by the aorta gradient, in order to avoid absurd coefficient values.

Operation groups II and IV (mitral valve operations). Duration of atrial fibrillation, "preoperative insufficiency", end-diastolic pressure in LV, preoperative blood flow, and squares of heart volume, work test and systolic pressure in PA.

Operation group III (combined operations on aortic and mitral valves). Aortic gradient, degree of insufficiency in MI, as well as squares of preoperative blood flow, heart volume and work test.

Operation group V (shunt cases except Fallot). Shunt in l/min, "other ECG changes". PCV at rest and squares of heart volume and work test.

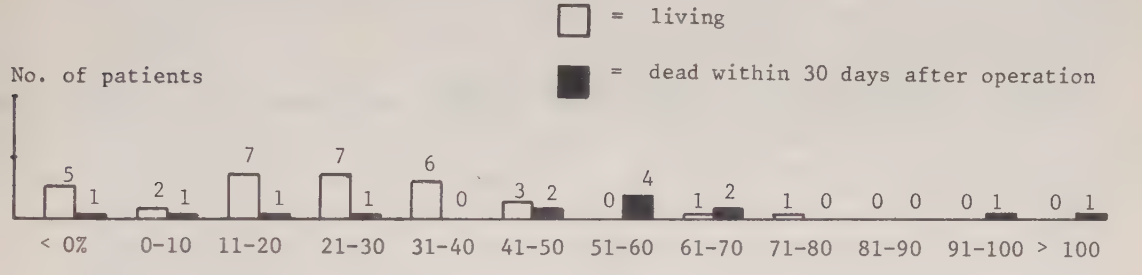
Operation group VI (Fallot´s tetralogy). Hb, gradient RV-AP, O_2 in aorta at rest, degree of RV hypertrophy on ECG and squares of heart volume and work test.

Operation groups I-VI were also included, in order to obtain a correct mutual relationship between the groups´ characteristics. However, operation group VI was deleted, in order to avoid singularity. The result of this analysis showed that the number of absurd coefficients was reduced but that the explanatory value was also reduced (R^2 = 0.386) and hence the accuracy of prediction. Thus, of the 191 patients in the material, eight fatal cases received predicted values of under 40 %, while 10 of those surviving obtained > 60 %, including 1 of 71 %. In a prediction according to this analysis, shown in Table 13 A-E, the percentage error was thus 7.5 % at predicted values under 40 % and 30 % at predicted values of over 60 %. For 6 of the 49 fatal cases, predictions of over 80 % were obtained, while 64 survivors received under 20 %. None of the survivors had over 80 % and none of the fatal cases under 20 %. The lower number of absurd coefficient values suggests that better generalization can be obtained with this system, or modifications of it, than with that shown in Table 12.

(c) In a third attempt, only operation group I was analysed separately in relation to the other patients. This analysis yielded the poorest results of all, with an R^2 of 0.145, thus showing a slight correlation between preoperative factors and mortality.

These attempts to base a forecast index on the material analysed, to be used for the prediction of the death risk, shows that the best result was obtained when preoperative data were selected from the final analysis and the xy correlation to-

gether (according to (b), above). This forecast index (Table 13 A-E) differs considerably from that shown in Table 12 (from the 31 regressors remaining in the final analysis). In the prediction (according to Table 13) of 46 cases operated on before (1962) or after (1965) the period of the investigation, the following results were obtained. It should be noted that these 46 patients were not exactly the same as those used earlier for the predictions in Table 12, in which operation group VII was included.



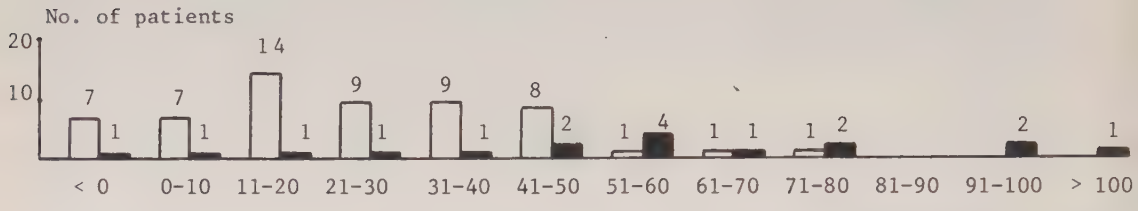
As is evident, 14 of the 46 patients died within 30 days of the operation. When a predicted value of 40 % was obtained, 4 of the 30 patients died, that is, the risk of error in prediction is 13 %. At a predicted value over 60 % the percentage error is 33 %. Thus, the prediction is impaired by the 4 fatal cases that had predicted values under 30 %. Of these 4, 3 were operated on during 1962 and 2 were the first patients operated on with Starr prostheses in both the aorta and the mitral valve, both with perfusion times of some 3 hours and with low cardiac output subsequently. The third patient (operation group I) had very poor right-sided coronary perfusion during the operation, and the fourth who was operated on in 1965 with a predicted value of -5 %, died 11 days after the operation of fungoid sepsis.

The prediction is also impaired by the 2 patients with values over 60 %, who survived the operation. Both these had a very complicated postoperative course with arrhythmia and long periods of respirator treatment. One of them later died while in hospital. This prediction agrees better with the risk figure than that shown in Table 12, which gives a very good prediction within the material analysed but worse when used outside. For a prediction according to Table 12, R^2 is thus 0.17 against 0.20 for Table 13. If, in the latter case, predictions are only made for patients from operation group I, R^2 becomes 0.27. Since R^2 for the predictions for the 191 patients in the material was 0.39, a deterioration has evidently occured. However, this deterioration is largely due to the patients operated on during 1962, before the start of the investiagion, when the technique used differed considerably from the present technique, amongst other things, in having inferior coronary perfusion during ECC.

If predictions are made only for patients from group I (from 1965), in accordance with Table 13 A, R^2 becomes 0.416, which agrees well with the correlation achieved when patients from the material analysed had their predictions taken from the forecast index (R^2 for group I was then 0.307).

Later predictions were made for a somewhat larger number of patients, according to the forecast index in Table 13. A total of 74 patients operated on in 1962 or in 1965-1966, i.e. before and after the investigation respectively, gave R^2 = 0.26

and 42 patients from 1965-1966 gave $R^2 = 0.25$, while 27 aorta cases during 1965-1966 gave $R^2 = 0.39$*. The distribution of the predicted values for all the 74 patients appears in the diagram below.



*The formula for calculating the correlation coefficient R is:

$$R = \frac{\frac{n_o \cdot S_1}{n_o + n_1} - \frac{n_1 \cdot S_o}{n_o + n_1}}{\left(n_1 \cdot n_o \cdot \frac{Q_1 + Q_o - \frac{(S_1 + S_o)^2}{n_o + n_1}}{n_o + n_1} \right)^{\frac{1}{2}}}$$

where n_o and n_1 are the number of survivors ($y = 0$) and fatal cases ($y = 1$), S_o and S_1 the sum of the predicted values, and Q_o and Q_1 the sum of the squares of the predicted values.

The formula is a special case of the formula for r, given in Ch. III B.

E. DISCUSSION

The analysis procedure described in this chapter involves the final obtaining of a small number of regressors by the reduction of a large number of preoperative variables. The former can then be used to predict the death risk. On the assumption that the ceteribus paribus principle applies (all other factors remain constant), an estimate of the importance of each factor is also obtained, partly in relation to other factors and partly with various types of heart operation. It appears from the analyses reported, however, that the combination of regressors that finally remains certainly has a very high explanatory value within the material analysed, but a particularly poor one outside it, that is, the conclusions cannot simply be generalized.

In order to obtain a good adaptation between the observed and the predicted values within the material analysed, certain regression coefficients are given paradoxical values, for example, the degree of aortic insufficiency. If it is desired to discover what this factor signifies in itself, it should preferably be analysed within a material consisting purely of cases of aortic insufficiency, but even then the result will apply only to this special material and cannot simply be generalized. Of course, the prediction of the death risk based on a large number of "pure" cases would be a better basis for a system of death risk prediction, but would be less applicable when it was desired to compare the preoperative status of patients belonging to different operation groups. To some extent, the difficulties of generalizing from the material analysed here are due to the fact that the number of patients is small in relation to the number of regressors. In the field of open-heart surgery it is difficult to assemble large and homogeneous patient materials, as developments have hitherto been so rapid that the indications and operative techniques have changed at short intervals. The method of analysis described, however, makes it possible for a material to be expanded continuously, for example, by making fresh analyses annually and taking possible changes into account. As the material grows, factors with genuine significance will come to have greater statistical significance, and those with misleading coefficient values or signs, will drop out or be corrected. In this way it is also possible to analyse the effect of changes introduced, while taking account of the patients´ preoperative status.

By being able to correct for preoperative status in various groups of patients, it is possible to judge more certainly the effect of the various changes introduced, for example, the composition of the prime, improved postoperative treatment, etc. If, for instance, a series of 20 cases were operated on with blood only in the priming volume of the oxygenator without fatal outcome, and 20 other cases were operated on without blood in the priming volume with 10 fatalities, one might reasonably suppose that the first method was the best. If, however, the expected risk according to the forecast index - including only preoperative variables - is on the average 0 % for the first group and 50 % for the second, the change in the prime has in actual fact had no effect whatever. This example shows that a simple forecast index that can be attached to the case record may be of great use. With such an aid, patients with similar risks can be chosen in pairs for, for instance, an experiment or drug test, and then the choice of treatment case and control case can be decided by lot between the pair. If the forecast index can gradually be constructed from large materials, such a satisfactory degree of generalization may be obtained that it can be used with reasonable safety for comparisons of materials from different clinics. For example, the average and scatter of the patients´ predicted values should be given when announcing the results of various experiments and methods.

Against this background, the discussion is intended to elucidate the following points.

(1) The deficiencies in the form of this analysis.
(2) The conclusions to be drawn from the analysis carried out.
(3) To what extent the attempts at generalization have succeded.
(4) How the system could be improved.
(5) Whether other systems could produce better results.

1. DEFECTS IN THE FORM OF ANALYSIS USED.

(a) Criticism of the regression methods. The type of regression analysis here applied has some serious disadvantages:

(1) When many regressors are analysed, as in this case, the risk of false significances is considerable, above all, at the 5 % level of error. If, for example, 200 irrelevant regressors are analysed, at this level of error 10 significant coefficients would be expected to be the result of chance. If 30 significant coefficients are obtained, it is quite conceivable that 20 of them are genuine, while 10 are false; the latter may have arisen by chance. To avoid false significances, it is possible to raise the significance level, for instance, to a 1 % level of error but this involves a risk that essential regressors may be excluded by mistake.

(2) As a result of the deletion procedure, one generally obtains too good a relation between observed and predicted values. As regards R^2 and RSD, which constitute a measure of the goodness of fit, one finds that it is difficult to repeat the results in applying the reduced equation to other material (cf. page

(3) Variables of the qualitative type, for example, the operation groups, which are seven in number:

I	Aortic-ostium operations	IV	Starr prosthesis in the mitral ostium
II	Plastic procedures on the mitral valve	V	Shunt cases (except Fallot´s tetralogy)
III	Combined operations on the aortic and mitral valves	VI	Fallot´s tetralogy
		VII	Miscellaneous operations

Here the number of simultaneously introduced regressors corresponding to these groups may be six at most (otherwise singularity arises). In practice, one group (the seventh) was taken as a basis, so that the regression coefficients became expressions of the magnitude of the difference between groups I and VII, II and VII, III and VII, IV and VII, V and VII, and VI and VII.

In spite of the deletion procedure, all these coefficients will perhaps remain. If another base group has been chosen instead, for example, group IV, the possibility of no coefficient remaining is not excluded.

(4) In order to make use of the WRAP programme, the missing values must be inserted, for instance, by simulation.

(5) The regression analysis can be misleading because of systematic errors in the variables.

(b) Significance of variations in individual variables.

Recording the preoperative data. The preoperative factors that were tested for each patient (see Ch. III) were supplemented, when necessary, in the way stated. This was done when the information was wholly lacking or a proper investigation was not carried out under the actual period of hospital care. It is necessary to supplement data while an omitted value is counted as zero, which produces a considerably greater error than if, for instance, the average for the operation group is inserted. The end-diastolic pressure in LV for the patients who underwent aorta operations was supplemented eight times (96 patients), by inserting the pressure measured during the operation before ECC. The HCO_3^- in serum was supplemented 10 times by inser-

ting the average for all 191 patients. Other final regressors were not supplemented at all or only in isolated cases. The supplementing was thus either slight or was carried out in such a way that the validity of the relevant factor was not changed because the averages were inserted. The end-diastolic pressure in the left ventricle in cases of aorta defect constitutes an exception; in this case the pressure measured during the operation before ECC was inserted. As a result of supplementing this factor may have had a greater significance than would otherwise have been the case.

Of probably greater significance than the supplementations are the preoperative variables that were not included in the analysis at all, for instance, the occurrence of anomalies of the coronary artery and/or coronary sclerosis. A direct expression for the preoperative condition of the myocardium is also lacking. Here only "preoperative insufficiency" (where group 3 means treatment with both digitalis and diuretics) was included in the absence of reliable criteria. The values for the contraction capacity of the left ventricle (diastolic minus systolic volume calculated radiologically) were available only for about half of the cases, and therefore judicious supplementing was impossible. In renewed yearly analyses, of course, such factors must gradually be taken into account as the number of patients with genuine values increases.

Effect of irregular error

In the present study only the results of the routine clinical methods used in the hospital (preoperative catheterization data, laboratory tests etc.) could be assembled, since it was impossible to "verify scientifically" the single factors in the large quantity of data recorded. It is, however, of interest to see how large an effect the presumably reasonable irregular errors in a number of regressors have on their coefficients, and thus on the result of the analysis.

Of the 31 final regressors, the following were considered, for the purposes of this investigation to have no irregular errors, as they were recorded in accordance with the definitions drawn up in advance: length minus weight, incapacity for work in years, addition of mannitol and Rheomacrodex to priming volume, number of diagnoses, congenital or acquired defect, degree of aortic insufficiency, and "other ECG changes". Other variables were considered to be subject to reasonable assumed errors, as follows (the assumed error means ± 1 SD in the determination of a series): the radiological method employed for measuring relative heart volume was assumed to have a reproducibility error of 5 % and the HCO_3^- and Cl^- in serum was assumed to have an error of ± 1 mE/l.

The end-diastolic pressure in the left ventricle in cases of aortic lesion has an irregular error of unknown magnitude. When moreover this variable was partly supplemented and partly squared it was assumed, as a reasonable figure for the error, that 1 SD of the determination error was 40 % (= 20 % in unsquared form). This implies that an end-diastolic pressure measured as 15 mmHg in 2 cases out of 3 was actually assumed to be between 12 and 18 mmHg. Similar limits were assumed to apply to the rest of the catheterization data.

Preoperative Hb. In the hospital laboratories 1 SD of the reproducibility in a Hb-determination is stated to be about ± 0.5 g%.

As is evident from Table 12 (the forecast index based on the final 31 regressors), these assumed variations within the regressors mean quite large changes in the predicted risk for the individual patient, for instance, in the combination of PCV and PA pressure in patients with mitral-valve defects, where deviations of a few mmHg in either direction may change the prediction completely. However, varia-

tions on account of irregular error would seem to be less important for the regression coefficients, which are obtained by analysis of patient groups. A greater irregular error implies, among other things, that a regressor has a slighter correlation and is therefore more easily eliminated during the regression analysis.

To ascertain the effect of the irregular errors, the following analysis was performed. The 31 final regressors were analysed at a p-level of 0.00, as already indicated. The computer was stopped when the XX matrix* had been formed, and this matrix was written out on punched cards. The cards bearing the sums of the squares of the variables with the assumed errors were extracted and these sums were reduced by the square of the assumed error (1 SD) multiplied by the number of patients. The new cards were again inserted and the analysis was completed in the usual way. Thus, the main diagonal in the equation system (see page 21) was corrected by this procedure.

The result of this intervention in the analysis shows the coefficient values that would have been obtained for the changed regressors, if these regressors had contained no assumed errors whatever of the order of magnitude which has been attributed to them here. A comparison between the results of this analysis and a comparable analysis with no assumed error introduced showed that the intervention led to considerable changes, in most cases increases in coefficient values, not only for the regressors containing assumed errors but also for other regressors, a few of which even exchanged sign (Table 14). In themselves, these changes are not noteworthy, when the combination of remaining regressors is adjusted so that the agreement between the observed and the predicted mortality is as good as possible. From the methodological point of view, this analysis is interesting, as it shows that a better prediction can be achieved if the irregular errors in the variables analysed can be reduced, and that by special analyses it is possible to find out the maximum irregular error that can be tolerated in the investigational methods used in clinical practice. From the practical point of view, in connection with the present investigation, this result would seem to be of less importance, partly because there is no reason to think that the magnitude of the irregular error was changed during the period of the investigation and partly because account had already been taken to some extent of the existing irregular errors, owing to the fact that these errors lower the significance level of the coefficients. However, one practical result of the analysis is the discovery that the levels of systematic and irregular errors must be checked continuously and that corrections must be introduced for possible large changes during the further annual analyses.

2. Conclusions to be drawn from the analyses carried out

From the inquiry in this chapter it is clear that the most marked correlation between preoperative factors and mortality is obtained if a moderate reduction criterion (p-level 0.80) is used, but that a large number of regressors remain. If the reduction criterion is raised, fewer and fewer regressors remain, but there is also a less marked correlation (lower R^2). The most suitable reduction criterion for this type of analysis would seem to be a probability level of 0.95, when the coefficients of all remaining regressors reach at least(*) significance, when R^2 is still high, when the number of absurd predicted values is significantly lower than at a p-level of 0.80 and the number of regressors that may be expected to retain their places by chance is reduced to at most 5 % of the original number of variables.

The result of the final analysis of preoperative data at a p-level of 0.95 shows that the combination of 31 regressors that remained may account to a very great extent for the mortality within 30 days with respect to the 191 patients in

*i.e. the sums of squares and cross products (see Features of WRAP, p. 26).

the material. The explanatory value is represented by the correlation coefficient R, which had a value of 0.754 in this analysis (R^2 = 0.569), which means that some 60 % of the fatal cases could be predicted on the basis of the patient´s preoperative status. That part of the question which was set forth in the Introduction and was intended to shed light on "the prognostic significance of preoperative factors for mortality within 30 days of the operation" may thereby be considered as having been satisfactorily answered, as regards for the material analysed. With the system described, this mortality can consequently be predicted with a fairly high degree of probability by the analysis of the preoperative factors. Unfortunately, the satisfactory result cannot be generalized, as a large number of final regressors have absurd coefficients and signs. These arose because in the combination of 31 regressors finally chosen from some 150 (milliards of combinations can be obtained from the expression $\binom{150}{31}$), they assumed values that gave the best adaptation to y within the particular selection of patients analysed.

As a result of the occurrence of these irrelevant regressors with absurd coefficients, the interpretation of the coefficients, whose values and signs are to a great extent specific to the present material, is made more difficult or impossible. However, a certain idea of the mutual relationship between different preoperative variables can be obtained from the final regressors in the various analyses. Thus it has emerged that the preoperative heart volume is the most important single factor, especially for operations on the aorta and combined operations on the aortic and the mitral valves, and that the preoperative Hb for cases of Fallot´s tetralogy, "other ECG changes" for other shunt cases, and the end-diastolic pressure in the LV for aorta operations, are the most important data for patients chosen according to the operation indications drawn up in Ch. II. The analyses also show that additions of mannitol alone or in combination with Rheomacrodex in the oxygenator of the heart-lung machine reduce the operational risk in comparison with the other primes used.

3. In what respects have the attempts at generalization succeeded?

The forecast index shown in Table 12 is based on the 31 regressors obtained in stage 2 of the final analysis. The steps within the classes are in this case so great that prediction within the material is satisfactory only if the patients´ respective values are interpolated, and if the irregular error is disregarded. Attempts to generalize (to predict for patients other than those included in the material) therefore produce unsatisfactory results.

The material analysed also formed the basis of the attempts made to construct a forecast index with better general validity. Thus the index given in Table 13 A-E can be used only on similar materials with the same or narrower operation indications. This index was obtained by analysing selected regressors for each operation group, that is, preoperative factors which have proved to have a strong correlation with postoperative mortality, either in the simple xy correlation or in the final analysis. This index also contains regressors with absurd coefficient signs, depending on the composition of the material analysed. However, it gives to a large extent the same prediction result both within and without the material, especially if the result for Table 13 A only (prediction for aortic-valve operations) is studied. Consequently this index can already be used for predicting mortality following operations on the aortic ostium, if the operation indications are approximately the same as those reported in Ch. II. This means that it is true to say that patients who have predicted values under 20 % have a very low mortality risk, and patients with values over 80 % are very unlikely to survive the planned operation.

4. How can the system be improved?

As already stated, a forecast index based on regression analyses of the type described, should be improved by increasing the number of patients. However, even the present system could probably be improved by a series of analyses in which, in the first place, regressors with absurd signs were exchanged for others or discarded, or certain operation groups were further subdivided. This was not done in the current study, as Table 13 A (forecast index for aortic-valve operations) contains only one regression coefficient with an absurd sign ("preoperative insufficiency" of grade 3 produces a reduced risk of death). It would be possible to exclude this regressor, as at present it modifies the effect of old age (as is evident from the very high primary xx correlation between these two variables). At the same time $(age)^2$ should be exchanged for age alone. The same procedure can be used in other parts of Table 13, as it is possible to read off in the xx correlations which "genuine" regressors are affected by those with absurd coefficient signs. This procedure, however, is costly when the best combinations must be worked out by means of repeated analyses, and the final result still depends on the material analysed. There is thus a primary justification for gradually increasing this material before the prediction system is revised. This index (Table 13) is considerably less sensitive to variations in the individual variables (for example, through irregular error) and can gradually be improved and extended by annual analyses of more and more patients. New variables can also be tested, together with those already chosen, and possibly included in a revised forecast index.

However, this index can already be used in its present form for the matching of patients, for instance, in experiments and the testing of drugs, except for patients in group VII, which is not included at all, and in group III, where the basis for the points system is only 12 cases. Other groups too should, of course, be gradually expanded for this purpose.

5. Could other systems produce better results?

As regarded the design of a forecast index, the classification involved certain difficulties, as has already been mentioned. Furthermore it is possible that other interaction factors should have been included. A system of analysis which may be more suitable in this connection than the one applied here has been introduced by Sonquist & Morgan (1964). For the prediction, their system selects the classifications and the combinations of factors which display the "best agreement" with the observed values of the dependent variable. It is difficult to imagine how this method would work if it was applied to a material of the type reported here, in which the large number of variables per patient exceeds the number of patients. It is conceivable that there might be a primary screening by the WRAP programme, followed by a final analysis by the system described by Sonquist & Morgan.

Another standard program, for regression analysis, is the Stepwise regression, (BMD02R), given in Biomedical computer programs (University of California, Los Angeles).

CHAPTER V

THE INFLUENCE OF PRE- AND PEROPERATIVE FACTORS ON THE 30-DAY POSTOPERATIVE MORTALITY

The object of this part of the investigation was to analyse the joint influence of the pre- and peroperative factors on the postoperative mortality, partly to illustrate the significance of each of these groups of factors, and partly to try and elucidate which peroperative factors have explanatory values, in addition to what can be explained by the preoperative factors. Data relating to the following peroperative factors were assembled (cf. Ch. III): perfusion, operation, drugs used, fluid and blood balance, acid-base status and other laboratory tests carried out during the day of the operation. For several reasons, postoperative factors were not included. Mortality is greatest during the first few days after the operation, which means that, as regards the fatal cases, data is lacking for most of the postoperative factors. Most postoperative factors are the result of the operation or other pre- and peroperative treatment strategy and the like. During the operation day, on the other hand, all the patients included in the material (191 cases minus 10 who died within 24 hours = 181) were alive and the data lacking had to be supplemented only to an insignificant extent.

The analysis was carried out according to the principles presented in Ch. IV, i.e. the preoperative data for the 181 patients were analysed in two stages at a p-level of 0.95, after which 33 regressors remained. Earlier investigation had shown that the maximum explanatory value was obtained by the combination of the regressors remaining after analysis at a p-level of 0.80. For this reason, 38 preoperative factors were analysed in a further two stages, together with as many peroperative factors as were needed to make up 80 x variables each time.

Thirty-three regressors remained after the final analysis, of which 22 were preoperative and 11 peroperative. All attained a$^{(*)}$ level of significance, according to the definition. As there is a considerable risk that factors have not been deleted due to chance after so many analyses, only those with t-ratios of over 3.36 (***), in which this risk is very small, are reported.

RESULT

The preoperative regressors were the number of diagnosis groups (both linear and squared), incapacity for work in years and heart volume (squared). In addition, for operation group I, there were congenital or acquired lesion, incapacity for work and degree of aortic insufficiency (squared), for groups II and IV, incapacity for work and heart volume (squared), for group III, incapacity for work, for group V, incapacity for work, Cl^- in serum and heart volume (squared), and for group VI, finally, incapacity for work and preoperative Hb.

The peroperative regressors were total operation time, re-operation on account of hemorrhage, weight alteration during operation (weight after minus weight before), duration of fall in BP below 80 mmHg during ECC and quantity of K^+ supplied during the operation day.

Commentary on Table 15

The coefficients for these 20 regressors with t-ratios over 3.36 are shown in Table 15, in which the preoperative regressors' coefficient values have been inserted for comparison, after final analysis of the preoperative factors alone, in accordance with Table 9. This shows that both the set of variables and the coefficients values in Table 15 agree well with those obtained in the analysis of the

191 patients and interpreted in Ch. IV (Table 9). The preoperative regressors will therefore not be interpreted again, but it may be noted that their coefficients scarcely changed during the two steps of the analysis along with the peroperative factors, which indicates great stability. The peroperative variables and their regression coefficients, on the other hand, require closer analysis, as they have not been discussed earlier. After the analysis of the preoperative factors alone for 181 patients, R^2 was 0.574, and after the final analysis of both pre- and peroperative factors 0.665. Thus the insertion of the latter certainly increased significantly(***) the explanatory value of the predictions obtained, in relation to the observed mortality, though the increase was moderate. In the former case 48 absurd predictions were obtained (42 below 0 % and 6 over 100 %), while 7 fatal cases received predictions of less than 40 %: in the latter, 62 absurd predictions were obtained (53 under 0 % and 8 over 100 %) and 4 fatal cases received predictions of less than 40 %. Occurrent and recorded peroperative factors thus raised the prediction values for 3 out of 7 fatal cases over the 40 % limit. Fig. 2 shows how the prediction changed for each of the 181 patients as a result of the insertion of the peroperative variables. It is clear that the greater proportion (26) out of the 39 fatal cases received higher risk numbers from the pre- and peroperative factors than when the preoperative status only was taken into account. It should also be noted that a small number of patients survived, in spite of the effect of unfavourable peroperative factors, and that no patient with a risk number over 50 calculated on the pre- and peroperative factors and only one calculated on the preoperative status only survived the operation for 30 days.

INTERPRETATION OF THE REMAINING PEROPERATIVE REGRESSORS

Of the approximately 100 peroperative variables analysed together with the preoperative variables, five with t-ratios of over 3.36 remained after the last step. Their coefficients had the following meaning.

Whole period of operation. This variable refers to the time from the commencement of anesthesia until the patient leaves the operating theatre. As is evident, a prolongation of the operation time by 1 hour increased the risk by 7 %. The operation time shows a high simple correlation (***) with y ($r = 0.308$). Since there was no significant positive correlation with any preoperative factor, and only one significant negative correlation (with operation group V), this shows that operative complications or other factors that extend the time of the operation make the prognosis worse, irrespective of the nature of the operation.

There is a significant, positive simple correlation between, on the one hand, the duration of the operation and, on the other, the following peroperative factors: period of cardiac arrest or aortic cross-clamping (*), number of DC shocks after this (*), arrhythmia after the operation (**), complications resulting from preoperative status (*), quantity of fibrinogen supplied during the day of operation (***) and Hb and hematocrit variations during the operation. Thus a longer operation time involves higher values, for these factors, and also for the pCO_2 during ECC. A significant, negative, simple correlation exists with the esophagus temperature during ECC, the quantity of K^+ administered, the number of thrombocytes during ECC, and the preoperative pH and pO_2 during the first few hours after ECC. All this shows that the cases with the longest operation times were the most complicated, both before, during and after ECC. Thus, in the result of the analysis the duration of operation variable represents a number of more or less serious operative complications, for instance, postoperative arrhythmia and postoperative hemorrhage resulting from lack of fibrinogen.

Re-operation on account of hemorrhage

This variable was recorded as either 1 (not re-operated) or 2 (re-operated) and therefore the risk in this material increased by + 55 %, if the subsequent hemorrhage was so severe that recourse had to be had to open hemostatic methods, as occurred in 8 cases among the 181 patients.

There was a significant, positive, simple correlation with bacterial growth in the machine blood, the quantity of fibrinogen supplied during the day of the operation, the Hb and hematocrit values before, during and after ECC and the pH after ECC. The distribution of re-operations by operation group, the oxygenator used and the prime is given in the table below:

Operation group	Oxygenator used	Prime	Mortality group
I	Disc	Blood + glucose	0
I	Disc	Blood + mannitol	3
II + IV	Bubble	Blood + glucose	2
III	Disc	Blood	3
V	Bubble	Blood + glucose	2
VI	Disc	Blood + Rheomacrodex	2
VI	Disc	Blood + mannitol	0
VII	Bubble	Blood	0

Weight alteration (weight after minus weight before the operation)

Each patient was weighed naked before the operation on an ordinary scale and afterwards in bed by means of a bed scale, employing a standard procedure evolved to give the minimum error. This variable has a very slight simple correlation with the mortality ($r = 0.0030$). The weight increased significantly during the operation among patients with several diagnoses and large heart volumes, in other words, among the severe cases of aorta defects and combined aortic and mitral-valve defects. The variable in the analysis received the opposite sign from that expected (1 kg weight increase reduced the risk by 4 %), which means that it damps the effect of some other variable, which, for these patients, acquired too great a significance in the analysis. There is a significant negative correlation with the urine quantity during the operation day, showing that patients who increased most in weight had the smallest urine quantity.

Duration of fall in blood pressure below 80 mmHg during ECC

Measurements of arterial blood pressure were taken in the femoral or brachial artery. The variable was given values from 1 to 7, as follows:

(1) No fall below 80 mmHg
(2) Blood pressure below 80 mmHg for 10 minutes
(3) Blood pressure below 80 mmHg for 20 minutes
(4) Blood pressure below 80 mmHg for 30 minutes
(5) Blood pressure below 80 mmHg for 45 minutes
(6) Blood pressure below 80 mmHg for 60 minutes
(7) Blood pressure below 80 mmHg for 1-3 hours

The coefficient is 0.0438, and therefore each step of the scale indicates a 4 % increase in risk. A patient with blood pressure below 80 mmHg for 60 minutes during ECC is thus at $6 \times 0.0438 - 1 \times 0.0438 = 22$ % greater risk than when the blood pressure has been maintained at over 80 mmHg. There is certainly a relatively marked, simple, positive correlation ($r = 0.128$) with the mortality, but this is not significant. As in the case of the weight alteration, there is a positive corre-

lation, as regards falls in blood pressure, with acquired defects and large heart volumes, and also with low capacity for physical work. Falls in blood pressure also occur more frequently among patients with operative complications, resulting from their preoperative status, and patients who have required a large number of shocks after cardiac arrest.

Supply of K^+ during operation day

The coefficient is - 0.106 and the recording relates to the quantity of K^+ supplied in mE/kg b.w. during the operation day. On the average, the 181 patients received 0.8 mE/kg b.w. This means that in this material the supply of potassium to the extent of 1 mE/kg b.w. during the operation day reduced the risk by -22 %. The supply of K^+ was greater during the latter part of the investigation, and therefore it is not out of the question that this variable in itself may involve a time factor. The correlation to the prime containing both Rheomacrodex and mannitol - a combination which was used only during the last part of the investigation period - is also remarkably high (r = 0.379). The correlation is also significant with several diagnoses and large heart volume.

Effect of other peroperative factors

Other significant peroperative variables, though at a lower level of significance (* or **) than those mentioned earlier, were left-sided coronary perfusion and size of Starr prosthesis in the aorta in operation group III, right-sided coronary perfusion in group I, and reduction of the pulmonary gradient in cases of Fallot's tetralogy. Significant peroperative variables in all the operation groups were the quantity of fibrinogen supplied during the operation day, the Hb and pCO_2 values before ECC, the hematocrit value during ECC and the HCO_3^- value after ECC.

MULTIPLE REGRESSION ANALYSIS BETWEEN PRE- AND PEROPERATIVE FACTORS

In order to investigate to what extent the remaining peroperative factors could be explained by the preoperative status of the patients, the following investigation was undertaken. The 38 remaining preoperative regressors at a p-level of 0.80 in stage 2, were regressors, and the five remaining peroperative regressors with t-ratios over 3.36 in Table 15 were dependent (y) variables (regressands) in an analysis at a p-level of 0.95. The results were as follows:

The entire operation period as regressand

Ten regressors attained a significance of (***) . This applied to the different operation groups, of which groups III and I had the longest and groups II, IV and V the shortest operation times. Greater heart volume also involved longer operation times within the groups. In this analysis R^2 was 0.313, and therefore there was a significant correlation between the operation times and the preoperative status.

Re-operation on account of hemorrhage (regressand)

Only two regressors with (***) significance remained in the analysis. Pulmonary hypertension among the cases of mitral defects and raised preoperative Hb among the patients with Fallot's tetralogy involved increased risk of postoperative hemorrhage of a degree requiring re-operation. R^2 in this analysis was only 0.185, and therefore re-operation because of hemorrhage was only to a small extent due to preoperative status.

Weight after minus weight before the operation (regressand)

In the analysis R^2 was 0.577, and therefore preoperative factors in this material had a great effect on the patient´s weight increase during the operation. It follows from the result that the explanation lies almost entirely in the number of diagnoses, so that patients with two diagnoses increased in weight much more than those with only one.

Duration of blood-pressure fall below 80 mmHg during ECC (regressand)

In the analysis R^2 was 0.103, and therefore occurrent falls in blood pressure had only a slight connection with the preoperative status. Only five regressors attained a significant level (*) . The importance of this was as follows. If blood was included in the priming volume, the blood-pressure fall was of shorter duration. Greater heart volume (**) involved a longer blood pressure fall for all except operation group I, in which a higher preoperative HCO_3 value instead involved a longer blood pressure fall (***).

Quantity of K^+ supplied during the operation day (regressand)

This variable cannot be assessed against preoperative status, as increasing quantities of K^+ were supplied during the latter part of the investigation, as is also clear from the high correlation to the prime with Rheomacrodex and mannitol, which was used only during the last part of the investigation period.

DISCUSSION

In the material of 181 patients analysed here, a large proportion of the fatal cases within 30 days after open-heart operations can be anticipated simply by analysis of the preoperative status of the patients. By inserting the peroperative factors also, the possibilities of explaining the observed mortality are significantly increased. However, the increase is comparatively small, as it should be expected that the causes of death would, to an even greater extent, be explained by the operative complications.

In the analysis carried out here, the entire increase in the explanatory value is represented by only five peroperative regressors, which have partly their own explanatory values and partly replace other factors deleted during the analysis. From the experience gained in the studies of methods in Ch. IV, it can be predicted that one or more of these five regressors would be changed for others if another material than that used here was analysed. Thus, it cannot be generally asserted that the effect of all peroperative factors will be taken into account by considering the combination which has given the best result in this case. If predictions are made for another material than that analysed here, according to the forecast index in Table 13, and in a later examination the five peroperative factors are also taken into account, as discussed above, we may expect a reduced improvement (about half) of the agreement between the predicted and the observed values that has been obtained here (measured by R^2).

It is also interesting to note that some of the peroperative factors, are deleted in the regression analysis because they have high correlations to the patients preoperative status. Their own explanatory values are thus small. Conversely, this shows that in investigations of solely peroperative factors account is nevertheless taken to a certain extent of the patient´s preoperative status via these factors.

From the analyses in which the five remaining peroperative regressors that attained a level of at least (***) significance constituted regressands, it was clear that the entire operation time, and the weight increase during the operation were significantly affected by preoperative factors, while the postoperative hemorrhage requiring re-operation and the extent of blood pressure fall during ECC had no such significant correlation. An increased supply of K^+ during the operation day proved to reduce the mortality significantly. For this regressor there is a positive correlation, as regards time, with the prime containing Rheomacrodex and mannitol and a negative correlation with the prime containing blood. When K^+ constituted a regressand, these regressors therefore appeared as the sole factors with marked explanatory values for the supply of K^+. A possible explanation is that a time correlation exists, and the interpretation can be expressed as follows. The simple correlation between the supply of K^+ -0.10 (r_1) and between mortality and the prime mentioned above -0.13 (r_2).

From the formula $(r_2 - r_o \cdot r_1)/\left((1 - r_o^2)(1 - r_1^2)\right)^{\frac{1}{2}}$, the partial correlation coefficient between the prime containing Rheomacrodex and mannitol and the mortality is obtained. When calculated numerically, this is -0.10. Since the correlation was formerly -0.13 it is clear that a portion of this correlation is probably an expression of an underlying factor, probably the time factor. This implies that the effect of the prime on mortality may be overestimated if it is studied solely by means of the simple correlation coefficients.

CHAPTER VI

RENAL FUNCTION FOLLOWING EXTRA-CORPOREAL CIRCULATION

The aim of this part of the investigation was to try to analyse the extent to which the renal function was affected after open-heart operations, whether it was affected by the different primes used and whether disc and bubble oxygenators were equivalent, as regarded their effect on the postoperative renal function.

The material consisted of the 181 patients described in Ch. IV and V, and the statistical analysis was carried out by the method of multiple regression described in the same chapters. In this analysis the pre- and peroperative variables reported in Ch. III were included as regressors. The dependent variable (y) was the postoperative renal function, which was assigned the values 1, 2 and 3, in accordance with the following classification (symptoms in the first 10 postoperative days):

1. No clinically demonstrable restriction in the postoperative renal function: no oliguria, serum K^+ below 5.0 mE and NPN above 40 mg% on one occasion at the most.
2. Clinically demonstrable disturbance of renal function: NPN above 40 mg% for at least 2 consecutive days, otherwise as 1.
3. Acute renal failure: oliguria or anuria, rapidly increasing serum K^+, NPN and creatinine.

This classification was inspired by that published by Yeh et al. and reported in Ch. I. As is evident, the limits of the y variable are discussible, especially that between groups 1 and 2, where the only difference is the NPN in serum above or below an arbitrary limit set at 40 mg%. A dependent variable in a regression analysis of this type must, however, be recorded in numerical steps which define a value for each of the patients included, and the postoperative renal function has therefore been denoted here by 1, 2 and 3, in accordance with the above classification. What the numerical steps should really have been was afterwards illustrated by a kind of check analysis, of which an account will be given later.

As regarded patients who had died, the autopsy records were examined and any microscopic slides of kidney specimens were re-inspected for comparison with the clinical classification of the postoperative renal function.

In order to illustrate other differences between the three groups with different postoperative renal functions, the mean values, SDs and SEs of the following postoperative factors were calculated: the extent of the NPN increase, the postoperative creatinine clearance, the ratios of the creatinine and urea concentration in urine and in serum, respectively, and the quantity of urine for each renal-function group*. Only the NPN increase was recorded for all the patients (days 1-5 + day 10), while values for the other factors were recorded four times during the operation day (before, during and after ECC while the operation was going on and during the remainder of the operation day) and on the morning of the first two days after the operation for 135 of the 181 patients.

A. THE STEPS IN THE ANALYSIS

The analyses were carried out as follows:

Step 1. Eighty preoperative factors were analysed at a p-level of 0.95. The remaining regressors (18) were used in Step 2.

Step 2. The remaining regressors from Step 1 were combined with interaction variables between themselves and the different operation groups. Twenty-one preoperative regressors remained after reduced regression.

* The creatinine clearance and the ratios creatinine or urea concentrations in urine/blood were calculated, for all periods during the day of operation, with the aid of respective serum-levels measured the next morning.

Step 3. The remaining preoperative regressors from Step 2 were analysed, together with the operation groups, the primes used and the bubble or disc oxygenator at a p-level of 0.00.

Steps 4 and 5. The combined effect of peroperative factors, and the remaining regressors in Step 2 (at a p-level of 0.80), was analysed as described in Ch. V at two p-levels (0.95 and 0.99).

Step 6. The remaining regressors from Step 5 were analysed, together with the operation groups, the primes and the bubble or disc oxygenator at a p-level of 0.00, in order to make it possible to interpret any possible differences between the primes and the bubble or disc oxygenator.

Special analysis. In order to assess the arithmetical steps within the y variable and to try to get an idea of the possibilities of generalization, the material was divided into two matched samples, designated Sample I (90 patients) and Sample II (91 patients), using each patient's operation risk due to his preoperative status in accordance with the final analysis in Ch. IV. The patients were matched in pairs, so that the pairs agreed as regards (1) the predicted death risk, based on the preoperative status, in accordance with the analysis in Ch. IV (in this connection a deviation of 10 % was tolerated in the first round), (2) the operation group, (3) the bubble or disc oxygenator and (4) the prime, after which chance decided which patient in each pair who was to belong to Sample I. It was possible to select about three-quarters of the patients as meeting all the criteria. When this selection could no longer be made, the criteria were discarded in the reverse order, until in the last four pairs the deviation in predicted value had to be increased to 20 %. These two samples were used in the following analyses.

In Sample I the preoperative data were analysed in several steps, as before (in this case, however, the number of regressors in each analysis was limited to 45 and the p-level was lowered to 0.85 because the material was reduced to half). After the final analysis 18 regressors remained. These were then analysed at a p-level of 0.00 together with the operation groups, the primes and the bubble or disc oxygenator, both for Sample I and for Sample II. The regression coefficients thereby became directly comparable.

In Sample II the dependent variable (y) was also varied, as follows:

$$y_1 = (y)^{1/10},\ y_2 = (y)^{1/5},\ y_3 = (y)^{1/4},\ y_4 = (y)^{1/3},\ y_5 = (y)^{\frac{1}{2}},$$

$$y_6 = y,\ y_7 = y^2,\ y_8 = y^3,\ y_9 = y^4,\ y_{10} = y^5,\ y_{11} = y^{10}.$$

As y previously had steps 1, 2 and 3, by this procedure the steps in $y_1 = (y)^{1/10}$ became small between the values 2 and 3 for y, while at $y_{11} = y^{10}$ the step between 1 and 2 became small compared with the step between 2 and 3. The value of R^2 was calculated, and in this way it was possible to determine how the steps between different y values should be chosen, so as to obtain the most effective correlation between the predicted and the observed y values.

B. RESULTS

1. The classification in three groups with different postoperative renal functions

Table 16 shows the number of patients in the three renal-function groups, together with the mean values and SEs of the residual-nitrogen values in the serum

preoperatively and on days 1-5 and day 10 postoperatively. As is evident, there are the following highly significant differences ($\bar{X}_1 - \bar{X}_2 > (SE_1^2 + SE_2^2)^{\frac{1}{2}} \times 3.3$): preoperatively between groups 2 and 3 but not between the others, on days 1-4 between group 1 and the others, and on day 5 and day 10 between all pairs of groups. Thus, highly significant differences were achieved between groups 2 and 3 only on days 5 and 10 in the postoperative course, which was probably due to the fact that the majority of patients in group 3 died in the first few days after the operation, before the NPN had reached a particularly high level. The last value obtained was then re-written for the following days, and thereby the average decreased and the SD increased. There was a clear difference the whole time between group 1 and the rest. In a smaller material (135 patients) the urine excretion, the creatinine clearance and the ratios between the urea and creatinine in the urine and blood were studied on four occasions during the operation day and during the first two days after the operation. The ratios for urea and creatinine for the operation day were obtained by comparing the concentration in the respective sample of urine with the concentration in the blood on the morning of the first day after the operation. The ratios for the first three samples were thus somewhat too low, as the concentration in the blood (as was shown by about 20 random samples) usually increased by 20-50 % between the afternoon of the operation day and the morning after the operation. The results of the comparisons between the three renal-function groups is shown in Table 17.

This table shows that there are the following highly significant statistical differences between the three groups:

Urine quantities: no differences at the (***) significance level but differences at the (**) level between group 3 and the others after ECC and later.

Creatinine clearance: between groups 1 and 2 during the remainder of the operation day and day 2; between groups 1 and 3 in all the periods measured; between groups 2 and 3 on days 1 and 2.

Urine/blood urea ratio: between groups 1 and 2 during the remainder of the operation day, day 1 and day 2; between groups 1 and 3 during the remainder of the operation day, day 1 and day 2; between groups 2 and 3 during day 1 and day 2.

Urine/blood creatinine ratio: between groups 1 and 2 during the remainder of the operation day, day 1 and day 2; between groups 1 and 3 during the remainder of the operation day, day 1 and day 2; between groups 2 and 3 during day 1 and day 2.

It is evident that for the creatinine clearance there are significant differences (***) during all the periods measured and for the urine/blood ratios of creatinine and urea for the remainder of the operation day and the following days, but for the urine quantities there are no differences which reach such a high level of significance, though the tendency is still clear as between group 3 and the others. Between groups 1 and 2 there are, as was expected, no differences, owing to the fact that in group 2 diuresis was maintained with mannitol whenever necessary.

In an attempt to determine whether previous kidney disease influenced the postoperative course as regarded renal function, the autopsy records of the 39 patients (out of 181) who died within 30 days of the operation were examined. In the case in which a microscopic slide had been produced at the autopsy, these slides were re-examined, taking into account, on the one hand, the time which had elapsed between the operation and death and, on the other, the time between death and the autopsy. Only 5 of the 92 patients belonging to group 1(no clinically demonstrable deterioration in renal function) had died within 30 days of the operation. Of the

74 patients in group 2, 20 died and in group 3 (15 patients) 14 died (the 15th patient died 5 weeks after the operation). Only 5 patients (4 in group 2 and 1 in group 3) showed more or less pronounced changes (nephrosclerosis or chronic pyelonephritis) which had been present before the operation. The microscopic examination showed that in practically all cases there were autolytic changes, which in a number of cases made it impossible to assess any intravital anoxic damage. If there was tubulus damage which was assessed as intravital, it was impossible to determine its degree. Thus here only cases in which there was probable or certain intravital tubulus damage are reported. In group 1 only one slide could be assessed (probably there was intravital damage). In group 2 ten slides could be assessed (five showed no, three probable and two positive intravital damage). In group 3 thirteen slides out of fifteen could be assessed (seven showed probable and six positive intravital tubulus damage of the tubular necrosis type (lower nephron nephrosis).

The analysis of the choice of steps 1, 2 or 3 in the y variable when the final preoperative regressors in Sample I were introduced into Sample II yielded the following results. When the y variable was varied continuously by altering the exponent from $(y)^{1/10}$ through y to y^{10}, a maximum for R^2 was obtained at $(y)^{1/4}$ but afterwards it fell very slowly at both sides. Thus, for $(y)^{1/10}$ R^2 was 0.309, for $(y)^{1/4}$ 0.311, for y 0.299 and for $(y)^{10}$ 0.254. It is clear from this analysis that, if group 1 is given a y value of 1 and group 3 a y value of 3, as was done originally, the value for group 2 will be about 2.20. Patients who have clinically affected renal functions, in accordance with the definition in this investigation, and who have been designated as 2 are thus on the average more like patients with acute renal failure than those with clinically unaffected renal functions postoperatively. The original grouping, with equal steps between the middle group and the other two, shows such a high value for R^2 in comparison with the best-transformed y variable that it constituted a regressand in the subsequent regression analyses also.

2. The effect of both pre- and peroperative factors on the postoperative renal function

(a) General factors. In the final analysis of the effect of the preoperative status alone on the postoperative renal function, a R^2 value of 0.536 was obtained, i.e. quite a high explanatory value for the remaining regressors. However, this value was obtained at the expense of interpretability, as several paradoxical coefficient values were obtained. In the final analysis (Step 5) of the pre- and peroperative factors at a p-level of 0.95, 26 regressors remained, of which eight were preoperative, and R^2 was 0.608; 19 absurd predicted values were obtained ($17 < 1$ and $2 > 3$). At a p-level of 0.99 (Step 5) only six regressors remained, but their explanatory value was considerably lower ($R^2 = 0.398$) after this raising of the reduction criterion.

As the postoperative renal function was divided into three steps, denoted by 1, 2 and 3, the coefficient values obtained cannot be translated into percentage risk. Instead the numbers obtained show the influence of the regressor on postoperative renal function, measured by the scale given above. In the final analysis (Step 5) at a p-level of 0.99, the remaining preoperative factors were $(\text{heart volume})^2$ (***) and $(\text{preoperative creatinine clearance})^2$. The regression coefficient for $(\text{heart volume})^2$ was $2.90 \cdot 10^{-7}$, and therefore 1000 ml/m^2 instead of 500 means that the risk of a postoperative renal damage is increased by 0.725 scale divisions. As the correlation with y was relatively slight in this analysis, the other remaining regressors will only be reported and not interpreted. The risk of postopera-

tive renal damage increased with a lower preoperative creatinine clearance (**), longer perfusion time (***), re-operation on account of hemorrhage (**), complications during the operation (**) and low excretion of urine during the operation day (***).

Comments on Table 18

As has already been mentioned, the 26 final regressors (Step 5) had a considerably larger explanatory value after the analysis of the pre- and peroperative factors at a p-level of 0.95, in which each remaining regressor achieved at least (*) significance. These regressors, their coefficient values and the level of significance are given in Table 18. In this combination, which yielded the best accommodation between, on the one hand, the pre- and peroperative factors and, on the other, the postoperative renal function in the material analysed, there are no less than 12 regressors whose coefficients only achieved (*) significance. Since the selection was made from over 200 variables, the majority of these 12 regressors may have remained by chance (5 % of 200 = 10). It is therefore not out of the question that the majority of the regressors which achieved (*) significance were of no real importance, and consequently they are not further discussed.

As regards the remaining regressors with (**) and (***) significance (eight and six respectively), the risk that they have remained by chance is considerably less, though this may be the case, at any rate as regards one or two of the former. However, it would seem to be possible to compare the influence of each of these regressors on the postoperative renal function and express it in scale divisions, according to the 1, 2 and 3 scale.

Six of the 14 regressors with at least (**) significance were preoperative. An acquired defect yielded +0.54 scale divisions, and a congenital defect 0. An increase of the preoperative heart volume from 500 to 1000 ml/m^2 represented +0.25 scale divisions, except for combined operations on the aortic and mitral valves, in which there was an increase of 3.51 scale divisions. Patients on whom mitral-valve operations had been performed had an improvement of 0.48 scale divisions compared with other surgical interventions. A preoperative creatinine-clearance value of 120 ml/min instead of 80 ml/min improved the prognosis by 0.18 scale divisions. For aorta operations, finally, the deterioration in postoperative renal function was 1.47 scale divisions greater if there was stenosis alone, compared with pure aortic insufficiency of grade IV.

Eight of the 14 remaining regressors with at least (**) significance were peroperative. The postoperative renal function was improved by a short perfusion time (1 hour shorter = -0.29 scale divisions), a higher mean value of the esophagus temperature during total perfusion (5° C higher = -0.03 scale divisions), a greater quantity of urine during the operation day (an increase of 10 ml/kg reduces the risk by 0.17 scale divisions), a higher number of Starr prosthesis inserted in the aorta in combined operations on the aortic and mitral valves (1 number higher = -0.20 scale divisions), a higher pH during ECC (7.40 instead of 7.30 = -0.09 scale divisions) and a higher HCO_3^- during the 3 hours immediately after ECC (1 mE higher = -0.06 scale divisions). Re-operation on account of hemorrhage made the prognosis worse by 0.55 scale divisions.

Comments on Table 19

In order to interpret the meaning of a regression coefficient, it is necessary to know to what extent the regressor is correlated to other regressors. Table 19 shows the primary correlation (simple xx correlation) between the 14 regressors with at least (**) significance, reciprocally and the simple xy correlation. Only correla-

tion coefficients greater or less than ± 0.10 were included, and the significance level for these was indicated by asterisks (other coefficients were denoted by ± ϕ).

It is clear from Table 19 that the 14 regressors are all more or less dependent on (or influence) each other.

Some aspects on coefficient interpretation

The coefficients are interpreted in different ways, depending on where in the causal chain (background factors--intermediate factors-- regressands) the actual regressor is placed. If the meaning of a pure background factor, such as congenital or acquired lesion, is to be interpreted, a single-factor analysis, in which this factor is the only regressor and the resulting factor the regressand, gives its real effect and yields the same level of significance as the simple xy correlation. If later, in the multiple regression analysis, the coefficient is lower in the unreduced regression, this means that a part of the factor's total effect is going via one or more of the other regressors included in the analysis. If, in the progress from unreduced to reduced regression, the coefficient increases in numerical value, this means that it is taking up the effects of regressors which have been deleted and that it will also continue to represent their effects on the resulting variable.

If the effect of an intermediate factor, for example, the length of the perfusion time, is to be interpreted, we can no longer rely on simple xy correlation or single-factor analysis, as it is not possible to read off from them the extent to which the effect of background factors is being channelled via the intermediate factor. In order to analyse this, the coefficient variation during multiple regression analysis must be studied. If the coefficient does not vary during the progress from unreduced to reduced regression, this means that the effect of the intermediate regressor on the resulting factor is real and not merely apparent (due to background factors), provided that the background factors with which there is a marked correlation (simple xx correlation) have been included in the analysis. However, there is a risk that one or more unknown background factors which have not been included in the analysis will have an effect both on the intermediate regressor and on the resulting factor, in which case a real effect may be mistakenly ascribed to the regressor. In that case the regressor may be designated as a symptom variable. If the coefficient of the intermediate regressor is obviously changed during the regression, this means that it will take over the effect of the regressors eliminated and/or channel its own effect via other uneliminated regressors. In that case these regressors may be traced via simple xx correlations and/or by stepwise changes in their coefficients during the regression. The partial regression and correlation coefficients may then be calculated and the significance of the real effect of the intermediate regressor may be assessed.

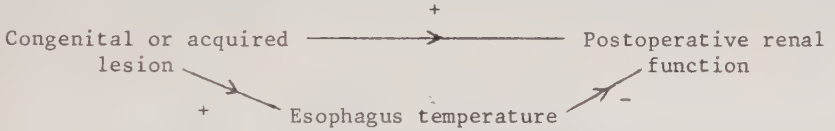
Interpretation of the highly significant coefficients in Table 18

As seen in Table 18, a number of regressors have larger explanatory values than others (higher t-ratios). The six which achieved (***) significance had the following t-ratios: "congenital or acquired lesion" 4.59, "$(\text{heart volume})^2$" 4.69, "perfusion time" 3.86, "minimum esophagus temperature during total perfusion" -3.70, "complications occurring during operation" 3.79, and "quantity of urine during the operation day" -4.53. Thus, all of them were considerably above the requisite value for (***) significance, which is 3.36.

It may therefore be of interest to try to analyse the reciprocal correlations between these six factors and between them and the regressand. It is essential to

investigate whether these six regressors have a real effect on the renal function or whether the effect is only apparent, i.e. the regressors are symptoms of background factors.

"Congenital or acquired lesion" will not be explained by any of the other regressors, as it is a genuine background factor. In the final analysis the regression coefficient after reduced regression was 0.535. It may be asked whether the effect of a congenital or acquired lesion is also exerted via other pre- and peroperative factors represented in the final analysis. If this was the case, the single regression coefficient with the renal function as regressand and the congenital or acquired lesion as regressor would exhibit a higher coefficient value. However, this coefficient is 0.363. One explanation of this lower coefficient value may be that patients suffering from Fallot´s tetralogy have a more impaired postoperative renal function than other patients with congenital defects. Since operation group VI (Fallot´s tetralogy) was itself eliminated in the analysis, its effect was transferred to the regressor representing the esophagus temperature during total perfusion (cases of Fallot´s tetralogy had lower temperatures than other cases). This argumentation can be illustrated by a schematic diagram which makes clear the causal connection (as regards the correlation coefficients and their signs, see Table 19):



Operation groups V and VI contain only congenital defects and groups III and VII only acquired defects. The final analysis showed that a further differentiation within these two pairs of groups was not necessary, as they were eliminated in the analysis.

Like the congenital or acquired lesion, the "(preoperative heart volume)^2" is a background variable. The circumstance that the heart volume was included among the final regressors in a squared and not in a linear form is an expression of the fact that it is primarily the large heart volumes that are important. Of course, from the point of view of interpretation, the heart volume is to be understood as indicating how serious the disease is. For this reason, it should be regarded against the background of the different diagnosis groups and consequently of the different operation groups. It is clear from the regression analysis that large heart volumes are of particularly great importance in cases of combined aortic and mitral-valve defects (operation group III), in which, however, the effect is mitigated by the fact that a large heart volume always involves the possibility of inserting a larger Starr prosthesis in the aorta (simple xx correlation 0.98). As regards patients who undergo mitral-valve operations, it is true to say that the effect of a large heart volume is mitigated by the fact that this group actually remains and has a negative correlation with y.

At the final analysis a regression coefficient of $3.28 \cdot 10^{-7}$ was obtained, while in the analysis in which (heart volume)^2 was the only regressor the coefficient value was $3.60 \cdot 10^{-7}$ and therefore the multiple and the single analysis yield results that agree well.

"The length of perfusion time". It is reasonable to interpret the relation between this regressor and the postoperative renal function as a real one. If the perfusion time was prolonged unnecessarily, it would be reasonable to expect an impaired postoperative renal function. However, it is not out of the question that

the correlation is only apparent and that it is caused by underlying factors that have effects on both the length of the perfusion time and the postoperative renal function. An argument in favor of the latter explanation is that the unreduced analysis in both Step 1 and Step 2 shows considerably lower and non-significant coefficients than the reduced analysis (0.00145 and 0.00477 respectively). A closer examination shows that half the difference is explained by the fact that the variables representing "the length of the whole operation time" and "the period of cardiac arrest" were eliminated in the final reduced analysis. These two variables are very closely associated and have a high degree of simple correlation with the length of the perfusion time.

A scrutiny of the progress from unreduced to reduced regression shows that the part of the difference which cannot be explained by the loss of these two regressors would seem to be related to preoperative factors which may conceivably have an effect on both the perfusion time and the postoperative renal function, probably the different operation groups. Thus, it is very likely that part of the correlation is only symptomatic but that part is real. It is clear from the simple xy correlation (Table 19) that the perfusion time shows a higher correlation than any other regressor (0.39). The corresponding regression coefficient (perfusion time the only regressor) is 0.00753. Since at the final and unreduced regression the coefficients were considerably lower (0.00477 and 0.00145 respectively), this illustrates that there may be quite large differences between the results of simple and multiple regression analysis. In the present investigation the length of the perfusion time thus had a genuine effect on the postoperative renal function, but at the same time background factors channelled a part of their effect on this function via the perfusion time(the simple xx correlation between perfusion time and shunt cases, except cases of Fallot´s tetralogy, was -0.35; between perfusion time and cases of combined aortic- and mitral-valve defects it was +0.34).

In the final step of the analysis the "minimum esophagus temperature" during total perfusion has a highly significant correlation (***) with the postoperative renal function (-0.00550). The simple xy correlation was -0.16 (*) , which agrees better with the coefficient in unreduced regression (-0.00289) and with the coefficient obtained when the esophagus temperature during total perfusion was the only regressor and the postoperative renal function was the regressand (-0.00382). The doubling of the coefficient value which comes about during the regression analysis is due to a series of correlations with other pre- and peroperative regressors, which were eliminated during the reduced regression. In addition, as was reported previously, part of the effect of the congenital or acquired lesion factor goes via the minimum temperature in the esophagus during total perfusion, which explains the difference from the simple correlation. Since the t-ratio for this regressor was -3.70 and at least half of the effect was assessed as being only apparent, it probably has no real significant correlation with the postoperative renal function. This is confirmed by the fact that the absolute value of the regression coefficient rises between the unreduced and the reduced analysis in Step 2, almost exclusively in connection with the fact that background factors are eliminated.

"Complications which occurred during the operation" have (***) significance in the simple correlation with y. The coefficient in the unreduced regression in Step 5 was 0.340 and after the reduced regression 0.339; thus there was no difference. When the complications were the only regressor, the coefficient was 0.423. The reason why the simple regression coefficient is greater than the unreduced coefficient may be that the same background factors as are correlated to operative complications also directly affect the renal function.

The "quantity of urine during the operation day" has (***) significance in the simple correlation with the postoperative renal function (-0.30). When the quantity of urine was the only regressor, the coefficient was -0.0189, in unreduced regression at Step 2 -0.0170. This stability in the coefficient shows that the regressor has, almost alone, a real correlation with the renal function, even though there are significant simple correlations with a series of pre- and peroperative variables, both remaining and eliminated. Thus, a small quantity of urine during the operation day has a significant simple correlation with an acquired lesion, a prime containing blood, a large increase in weight during the operation, a large number of white blood cells during ECC and a high pCO_2 during ECC. On the one hand, the quantity of urine during the operation day has an indisputably real correlation with the postoperative renal function and, on the other, it is influenced by a long series of other variables in both a positive and a negative direction. By way of summary, it may therefore be said that a significantly improved renal function may be expected postoperatively, if the diuresis can be kept high or normal during the operation day by neutralizing the influence of factors which produce tendencies to oliguria. Thus, in this investigation a large quantity of urine had a highly significant correlation with a prime containing Rheomacrodex and mannitol or mannitol (0.52), the normalization of the systolic RV pressure after correction of Fallot's tetralogy, a greater quantity of Tris supplied during the operation day, together with high values of pO_2 and HCO_3^- after ECC.

(b) Comparison between the bubble and the disc oxygenator

Of the 181 patients, 56 were operated on using the bubble oxygenator and 125 using the disc oxygenator. As was reported in Ch. II, there were various indications for the selection of patients, so that the "most serious" cases were always operated on using the disc oxygenator. An examination has shown that only 50 of the cases operated on using the disc oxygenator should have been operated on using the bubble oxygenator, according to these indications. During the perfusion the Hb and hematocrit values were significantly lower during ECC and these two values and the thrombocytes were significantly lower 5-15 min after ECC when the bubble oxygenator was used (greater hemodilution). On the average, the pCO_2 was also lower during ECC in these cases but not significantly so (higher gas flow). These differences are levelled out in the multiple regression analysis, if the ceteris paribus principle applies.

At Step 3 in the analysis (see page 60) the operation groups, the primes used and the bubble or disc oxygenator were added to the remaining preoperative regressors, after which multiple regression analysis was performed at a p-level of 0.00. From this it should be possible to read off directly the mutual relationship between the effects of the bubble and the disc oxygenators on the postoperative renal function, taking into account the patients' preoperative status. The regressor was recorded as 1 (=disc oxygenator) or 2 (=bubble oxygenator). The coefficient is -0.146, and therefore the disc oxygenator produces a risk of renal damage that is 0.15 scale divisions higher. At Step 6 in the analysis the operation groups, the primes and the bubble or disc oxygenator were analysed in a similar fashion, taking into account both pre- and peroperative factors (the regressors remaining from Step 5). With the introduction of the peroperative factors, the disc oxygenator came to appear as the better machine, as the favorable effect of the bubble oxygenator was then transferred to the quantity of urine during the operation day. However, the bubble- or disc oxygenator regressor then had a t-ratio of 0.15, i.e. far below the significant level.

(c) Influence of the addition of Rheomacrodex and/or mannitol to the priming volume

As in the case of the bubble or disc oxygenator, Steps 3 and 6 of the analysis can be used for comparisons between the primes used. The distribution of these primes has largely been shown in Ch. II. The comparison below was made from Step 3 in the analysis, as otherwise differences are caught up by stronger peroperative factors, such as the quantity of urine during the operation day.

In Step 3 the following regression coefficients were obtained:

Prime consisting of blood alone	-0.171
Prime containing blood	-0.297
Prime containing Rheomacrodex	-0.116
Prime containing mannitol	-0.258
Prime containing Rheomacrodex and mannitol	-0.030

The following total coefficient values for combinations of these primes were obtained from the way in which they were recorded:

Blood alone	-0.468
Blood + Rheomacrodex	-0.413
Blood + mannitol	-0.555
Blood + Rheomacrodex + mannitol	-0.701
Rheomacrodex + mannitol	-0.404
Blood + glucose	-0.297
Mannitol	(-0.258)*

All the coefficients are negative and thus favorable in relation to an imaginary group of patients who were assigned neither blood, Rheomacrodex nor mannitol. If the SEs for these coefficients are calculated, it appears that there are no indubitably significant differences between the various combinations. The distribution of the observed values is shown in Table 20. Judging from these values alone, the primes containing blood and Rheomacrodex and blood and glucose seem undoubtedly to be the worst and the prime containing blood, Rheomacrodex and mannitol to be the best. From the regression coefficients it also appears that the former involved a comparatively greater risk of postoperative restriction of renal function than the latter, taking into account all the preoperative factors included in the analysis, but that the differences are not significant.

However, if we treat the material in the conventional way and examine the correlation between mannitol, oliguria during the operation day and the outcome of the operation, we get the following results. Of the 107 cases in which mannitol was not included in the priming volume, oliguria appeared in 26 (24 %) during the operation day (hourly urine < 15 ml); of the 74 cases in which mannitol was included in the priming volume, on the other hand, oliguria only appeared in 3 cases (4 %). In these 3 cases, extra mannitol was supplied, and all 3 were classified in renal-function group 2. Of the 26 cases in which no mannitol was supplied in the prime, 2 occurred before mannitol began to be used (the first 23 cases in the series); 1 was classified in renal-function group 2 and 1 in group 3. The other 24 cases were distributed as follows: 6 in renal-function group 1, 12 in group 2 and 6 in group 3. The 26 cases (out of 107) in which oliguria occurred had primes with the following compositions: 9 (out of 19) had blood + glucose, 9 (out of 38) had blood only, and 8 (out of 50) had blood + Rheomacrodex.

In 4 of the 6 cases in renal-function group 3, in which mannitol was given during the operation day, no effect at all was obtained; anuria ensued within a few

* The last group contains only 1 patient, who died shortly after the operation of a low cardiac-output syndrome, combined with acute renal failure, which explains the low coefficient.

hours and the patients died of a low cardiac-output syndrome, in which anuria was an element. In 2 cases slowly decreasing quantities of urine were obtained for 24 hours or so, until anuria set in. All the other cases responded to the administration of mannitol, although 4 again developed anuria later, in connection with death due to left-ventricular failure or attacks of ventricular fibrillation.

As regards the cases in which oliguria arose during the operation day, the above analysis may be summarized as follows:

Prime	Renal group	No. of cases of oliguria	Cases treated with mannitol	Mortality within 10 days	
Blood, blood + Rheomacrodex, blood + glucose (107 patients)	1	6	6	1	Diuresis on administration of mannitol
	2	13	12	3	
	3	7	6	6	No diuresis on administration of mannitol
Blood + mannitol, blood + Rheomacrodex + mannitol, Rheomacrodex + mannitol, mannitol (74 patients)	1	0	0	0	
	2	3	3	2	Diuresis on administration of mannitol
	3	0	0	0	

Prime with no mannitol (10 fatal cases): group 1, 1 (24-48 hours after the operation); group 2, 3 (on days 3, 4 and 7); group 3, 6 (5 between 24 and 48 hours after the operation, 1 on day 5)

Prime with mannitol (2 fatal cases): group 2, 2 (both died between 24 and 48 hours after the operation)

A comparison between the cases in which mannitol was included in the priming volume and those in which mannitol was not included yields the following results:

		No. of patients	No. who died within 10 days	Renal-function groups 1	2	3
Oliguria during operation day	No mannitol in prime	26	10	6	13	7
	Mannitol in prime	3	2	0	3	0
No oliguria during operation day	No mannitol in prime	81	13	41	34	6
	Mannitol in prime	71	6	45	24	2

This table shows that both the mortality and the postoperative renal function were de facto more favorable if the patient was induced to excrete a large quantity of urine during ECC and during the hours immediately following ECC.

Can the results obtained be generalized?

In connection with one of the special analyses already described - the one in which the material was divided into two samples - an attempt to generalize the results was made. In this case the preoperative variables for 90 (sample 1) of the 181 patients in the material were analysed, as above, after which the final regressors obtained were inserted in sample 2, together with the operation groups, the primes and the bubble or disc oxygenator. The effect was the same as when predictions were made for patients who were not included in the analysis, in accordance with Table 12 in Ch. IV. For the 91 patients in sample 2, the 28 regressors were analysed at a p-level of 0.00. After the final analysis of the preoperative factors in sample 1, the remaining regressors showed a marked correlation with y (R^2 = 0.614, residual variance 0.202), but a large proportion of the coefficients could not be interpreted on account of their paradoxical signs. In the conversion to sample 2, the explanatory value fell in an obvious manner (R^2 = 0.299, residual variance 0.394), but at the same time the possibilities of interpreting the regressors were improved. However, the coefficients of these regressors did not reach a significant level and are therefore not reported. This test regarding the possibilities to generalize obtained results was thus made on only half the material. Nevertheless it shows that general conclusions should be drawn from highly significant results only.

C. DISCUSSION

In the present chapter the method of multiple regression analysis described in Ch. IV was applied to the material, with the postoperative renal function as the resulting factor (regressand). In previous attempts, in which the mortality within 30 days of the operation was the dependent variable (Ch. IV and V), a number of paradoxical regression coefficients were obtained, probably partly due to the fact that certain remaining regressors took on values which gave the best adaptation to the material analysed, with regard to the two steps in the y variable (0 and 1). When the y variable is further differentiated - as in the case of the postoperative renal function, which was divided into three groups - the paradoxical regression coefficients largely disappear. However, the goodness of fit is better for the mortality than for the postoperative renal function. In this work the patients were divided into three groups, according to the clinical assessment of the renal function within the first 10 postoperative days. The best defined is group 3, which is characterized by rapidly onsetting anuria, hyperkalemia and azotemia and by the fact that mannitol had no effect on the oliguria. This group comprised 15 patients, all of whom died within 5 weeks of the operation, and in most cases the autopsy findings confirmed that intravital tubular damage had been present. The borderline between the other groups (1 and 2) is discussible. As reliable clinical data were not available for all patients, the only difference between groups 1 and 2 was that patients with increases of over 40 mg% in the non-protein nitrogen (NPN) in the blood for 2 or more days in succession were placed in group 2. However, this applies to a relatively small number of cases; most of the 74 patients in group 2 had considerably more severe azotemia and often tendencies to oliguria and increases in K^+. However, it was possible to cure the two latter symptoms with mannitol and an ion-exchange resin respectively. As regards definition, all the cases could easily be assigned to any of the three groups.

The irregular error in the NPN analyses may, of course, mean that isolated cases were wrongly classified. More serious objections may be made to the choice of definitions, as regarded borderlines between groups. Thus, for example, it may be objected that the NPN value is not specific of the postoperative renal function (e.g. dehydration). However, there would seem to be no doubt that the great majority of the patients in the three groups differ also as regards other indicators of the postoperative renal function than those included in the definition. This is clear from Tables 16 and 17, which show that in group 2 all the means of measuring results are a compromise between what has been called here "unimpaired postoperative renal function" (group 1) and "acute renal failure" (group 3). The y variable, which was assigned the values 1, 2 and 3, should really have been noted as 1, 2.20 and 3, in accordance with the special analysis made of two samples of the material, which indicates that groups 2 and 3 are really closer to each other than the clinical assessment shows.

Thus, it would seem to be possible to assert on good grounds that the clinical division into three groups with different postoperative renal functions is adequate for its purpose, viz. to analyse which pre- and peroperative factors influence the postoperative renal function.

The result of the multiple regression analyses showed that the preoperative factors have a great influence on the postoperative renal function, though this influence is relatively less (compared with that of the peroperative factors) than they have on the mortality. In the final analysis, at a p-level of 0.95, 26 regressors remained, of which only eight were preoperative, with at least (*) significance. Of these 26, 14 reached a significance level of at least (**) . Only a few of them could have remained by chance and therefore the significance of only these 14 regressors has been reported. It should be pointed out that the increase or decrease of the risk of postoperative renal damage which has been stated applies only to the material analysed here according to the principles applied. However, in this material two preoperative variables turned out to be the most important when an analysis was performed at a p-level of 0.99 - the preoperative heart volume and the preoperative creatinine clearance. It is interesting to note that the preoperative creatinine clearance, which, on the one hand, has a large irregular error and, on the other, was supplemented 59 times in 181 cases in this work (mean values were introduced), nevertheless asserts itself with (***) significance. This shows that the creatinine clearance has a great prognostic value. As in the analysis of the influence of the preoperative factors on mortality, the preoperative heart volume proved to be the most important individual factor.

The 14 remaining regressors with (**) significance in the analysis at a p-level of 0.95 are all (except the preoperative creatinine clearance) combined with a network of correlations, and therefore their significance must be interpreted via these correlations. Examples of such an interpretation have been given for the six which reached (***) significance and thus could not have remained by chance. The following results were obtained. Acquired defects involved considerably greater risk of postoperative renal damage than congenital defects, in which Fallot's tetralogy, however, involved greater risk than other defects. A large heart volume with an acquired defect increased the risk, though insignificantly for patients with mitral-valve defects. Pure aortic insufficiency involved considerably less risk than aortic stenosis. Re-operation on account of hemorrhage greatly increased the risk. Probably long perfusion time, low esophagus temperature during total perfusion, a low value of HCO_3^- in the first few hours after ECC and a small quantity of urine during the operation day also had real negative effects on the postopera-

tive renal function. However, the peroperative regressors were partly indications of background factors, as was clear from the coefficient interpretation.

The following facts emerged from the investigations which were made as regarded the bubble or disc oxygenator and as regarded additions of Rheomacrodex and/or mannitol to the priming volume. When account was taken of the preoperative status and the primes used, the two oxygenators proved to be equivalent, as regarded the postoperative renal function. The addition of mannitol, alone or in combination with Rheomacrodex, to the priming volume yielded the best result, followed by blood alone, blood + Rheomacrodex, Rheomacrodex + mannitol without blood and, last of all, blood + glucose.

Though the differences between the various primes used here are not significant when account has been taken of other preoperative factors (probably because the material was too small), oliguria appeared very seldom during the operation day, if mannitol was included in the priming volume. When it did, in 2 cases out of 3 it was as an element in a low cardiac-output syndrome, which could not be cured. When mannitol was not included in the priming volume, oliguria during the operation day was common. It could usually be cured with mannitol, except when it was an element in progressive postoperative heart failure (6 cases, in 1 of which the patient died immediately after oliguria had set in and there were no criteria which made it possible to classify the case in renal-function group 3). In 2 cases, however, the oliguria could not be cured, in spite of the fact that there was no manifest low cardiac-output syndrome present. A comparison between patients who were operated on with and without the addition of mannitol to the priming volume shows that there was both lower mortality and a more favorable distribution of cases in the renal-function groups, if mannitol was used, even among cases in which oliguria did not appear during the operation day.

It was pointed out by way of introduction that the division into three renal-function groups was inspired by a report by Yeh et al. (1964). The reason for this was that these authors' material and methods largely conformed with those used here. Thus, their material consisted of 180 patients, 170 of whom were operated on using the disc oxygenator. Simple correlation analysis was used, as well as computer treatment of the data. There were also important differences, in that most of their cases involved congenital defects (139 cases) and a large number were children under the age of 15 (average age 17.5 years). In addition, all patients who died within 48 hours of the operation were excluded from the analysis, as against 24 hours in the present work. However, the most important differences probably lay in the fact that only peroperative factors were analysed, no account was taken of preoperative factors and multiple regression analysis was not used. The authors found that renal complications were virtually non-existent, regardless of other factors, if either the flow rate was kept above 2.2 $1/m^2/min$, the pump time was below 30 min or the hemolysis was below 50 mg%. On the contrary, it was found that no factor alone always involved renal complications but that a number of factors alone or in combination were often correlated to renal damage. These factors were low flow rate (< 1.8 $1/m^2/min$), perfusion prolonged over 60 minutes, hypothermia (below 89° F) when combined with low flow, hemolysis in excess of 200 mg% and postoperative acidosis (pH below 7.25).

In the present work these peroperative factors were included in the regression analyses, along with many other pre- and peroperative factors. As regards the length of the perfusion time and the degree of hypothermia, the results agree in part with those of Yeh et al., though these factors are to some extent symptoms for background factors. On the other hand, the flow rate, degree of hemolysis or postoperative pH have not, by themselves, had any significant influence on the postoperative renal function, when other pre- and peroperative factors were taken into account.

In the material analysed here the flow rate had a significant negative simple correlation (**) with the postoperative renal function, the perfusion time and the operation time and a positive simple correlation with the Rheomacrodex prime (which accordingly had a higher rate of flow than the other primes). On account of these correlations the significance of the flow-rate regressor was taken over by the above-mentioned regressors, after it had been eliminated. The degree of hemolysis had a very slight, simple correlation with the postoperative renal function and was rapidly eliminated in the analysis; the same remark applied to the pH in the first few hours after the operation. On the other hand, the complications which arose during the operation and the quantity of urine excreted during the operation day proved to have significant correlations (***) with the postoperative renal function.*

This comparison shows that simple correlation analysis is inadequate when the significance of individual peroperative factors is to be assessed. Multiple regression analysis must be performed and the results interpreted, taking into account the preoperative factors.

Doberneck, Reiser & Lillehei (1962) analysed the frequency of renal damage in a material of 1000 patients, most of whom had been operated on using the bubble oxygenator. It was found that 30 patients (3 %) fulfilled the criteria drawn up for renal damage, viz. oliguria (< 600 ml/24 hours for an adult), definite chemical evidence of azotemia (BUN in excess of 25 mg per cent) or hyperkalemia (serum K^+ in excess of 5.5 mEq per liter). The mortality amongst these cases of renal damage was 87 %. Attempts were then made to analyse in this material "the influence of open-heart surgery and total body perfusion on the production of renal failure". This was done by calculating the frequencies with which certain factors appeared among the 30 patients with renal damage and comparing them with the corresponding figures in the whole material. Significant over-representation in the renal-damage group was found for falls in blood pressure below 80 mmHg, both during and after ECC, and postoperative arrhythmias (atrial or ventricular fibrillation, total block and VES). Renal failure could be traced back to low cardiac output in all the cases. There was also over-representation of the pathological findings in the urine before the operation, in the form of proteinuria and/or a pathological sediment. As regarded the nature of the lesion, an obvious over-representation of Fallot´s tetralogy and mitral-valve defects (the only acquired defects in the material) was found. On the other hand, there were no significant differences as regarded age, degree of hemolysis, degree of acidosis (pH of arterial blood taken immediately after ECC), perfusion time, period of cardiac arrest or rate of blood flow reached during perfusion.

A comparison between the results from Doberneck, Reiser & Lillehei´s material and those from the present investigation shows good agreement, as was expected, especially with regard to the background factors, but also with regard to the recorded intermediate variables. The difference between the great significance shown by the fall in blood pressure in the material of Doberneck, Reiser & Lillehei and that in the present material, in which this regressor only achieved (*) significance, is explained by the fact that in many cases in the present material it was possible to neutralize the effect of falls in blood pressure by maintaining diuresis with mannitol, and in the process the patients came to be classified in renal-function group 2 instead of group 3. As regards the arrhythmias, which in the present work are included among the operative complications, the results are in agreement.

The above materials (Yeh et al. and Doberneck et al.) have been compared with the present material because the first was fairly similar and the second very large;

* Means ± SD of observed values for some peroperative factors are given in Table 21.

fully comparable works using multiple regression analysis have not been found in the literature. As was pointed out by way of introduction, there are sometimes such large differences between various materials and methods that comparisons are quite out of the question. In addition, the generalization of the results - other than highly significant and correctly interpreted results - would seem to be doubtful, even when account is taken of other pre- and peroperative variables, with the aid of multiple regression analysis. The work presented here has shown that, in the material analysed, spontaneous diuresis or diuresis maintained by therapeutic means provides a significant protection against postoperative renal damage. This effect may be explained by the theory presented by Steenburg et al. (1965), which involves the reduction of the "urea trapping" in the kidney (see Ch. I), and/or by the theory summarized below.

When account was taken of both pre- and peroperative factors, it emerged from this material that a high rate of diuresis during the operation day was very significantly correlated with improved postoperative renal function, and that both the mortality and the restriction of renal function were reduced if oliguria did not arise during the operation day or if it was cured by the administration of mannitol. Renal damage, leading to oliguria and anuria during the operation day, in spite of mannitol therapy, arose in most cases in connection with the low cardiac-output syndrome, and this in its turn had a considerably more marked correlation with background factors than with the peroperative variables analysed, except the operative complications. The present findings argue that the maintenance of diuresis has a positive protective effect when the kidney has been subjected to the trauma involved in open-heart surgery and ECC. The mechanism may be that indicated by Parry (1965), viz. that, if diuresis is in progress, it prevents the tubuli from being obstructed by precipitated proteins. Parry points out that factors such as ischemia, vasoconstrictive mechanisms, intrarenal shunts, circulating amines and increased renal resistance have not been shown to be of sufficient severity to be the direct cause of organic injury in acute tubular necrosis. He also states that direct krypton-85 or xenon-133 gas measurements indicate that renal blood flow is not significantly reduced, contrary to earlier clearance data. While reduced blood flow may create a functional disturbance leading to reduced tubular flow, the precipitation of normally soluble proteins, initiating the accumulation of mechanical impediments, seems the more likely cause of direct damage by obstruction. Patel, Mc Kenzie & Mc Queen (1964) have shown both in vitro studies and in human beings that a mucoprotein produced by the renal tubule epithelium can cause the renal tubular obstruction. On the whole, it is, however, very difficult to find correlations between functional and morphological findings in acute renal failure (Brun & Munck 1964).

These theories fit the findings in the present work well. The diuresis during the operation day proved to be the only really important factor for good postoperative renal function, while the degree of hemolysis, the duration of the fall in blood pressure and the degree of acidosis did not impair the postoperative renal function significantly. From this it follows that fluid restriction should be avoided preoperatively, that the production of urine must be watched continuously, that primes which produce a high rate of urine excretion should be used and that diuresis must be maintained as far as possible, with regard to the cardiac output.

CHAPTER VII

GENERAL DISCUSSION AND SUMMARY OF ESSENTIAL FINDINGS

The investigation presented in Ch. II-VI was undertaken since it proved to be almost impossible to transfer the results of hemodilution experiments from in vitro studies and animal experiments to a clinical material of patients who had been operated on routinely with the aid of ECC. This was on account of the great differences which existed between patients as regarded their preoperative status and the treatment given. Attempts were made to overcome the difficulties by using multiple regression analysis. This statistical method is intended to isolate the effect of individual factors, while taking account of all the other factors included in the analysis. The aim of the investigation has been described in the Introduction, the patient material, the principles on which this material was selected and the routine treatment in Ch. II, the factors included in the analysis and the statistical method in Ch. III and the results in Ch. IV-VI. This general discussion is intended to provide a summary of each of the preceding chapters and a short commentary on them.

A short conspectus of the relevant literature was given in Ch. I. However, the purpose of this conspectus was not to cover all the literature in detail but to provide a general list of background reading for the further exposition. In order to illustrate the difficulties in comparing the patient material, mortality figures, etc. as between different clinics, a collocation of such data, taken from a small number of publications, has been given in Table 1.

Chapter II contains a survey of the clinical material (191 patients) which was analysed. In addition, there is a description of the general indications according to which the patients were selected for open-heart surgery and the special indications according to which they were selected for the investigation (for example, only patients over the age of 14 were included). Naturally patients with other serious diseases (for example, diseases of the liver, kidneys, etc.) were not operated on. All the patients included in the material were operated on, using the same heart-lung machine, over a period of 2 years and 8 months, beginning in September 1962, and all the operations were performed by the same surgeon. Seventy-four patients who had received similar treatment in the period immediately before and the period immediately after the investigation were used in attempts to generalize certain results. During the final year of the investigation the bubble oxygenator and the disc oxygenator were used alternatively (previously only the disc oxygenator had been used). The indications for the choice of oxygenator have been specified in Ch. II, in which the techniques used for perfusion, anesthesia, postoperative treatment, etc. are also described. The material has been summarized in Tables 2 and 3; the patients are divided in Table 2 into five groups according to diagnosis (each patient may be included in several of these groups) and in Table 3 into seven groups according to the type of operation performed (each patient can only belong to one of these groups). These divisions were, of course, made before the series of analyses was commenced and could not be altered later without altering the whole series of analyses. On that account there are certain defects in these divisions, a matter which will be discussed later.

In Ch. III an account is given of the data (variables), which were first listed for each patient, then punched on cards and finally transferred to magnetic tape, after which they were included in the series of regression analyses made with the help of a computer (CDC 3600). These variables were divided into four groups: preoperative variables, comprising general information about the patient and his

disease and the results of general and special preoperative analyses; peroperative and postoperative variables, referring to the type of operation, data about the perfusion, checks during the operation and various data on the postoperative course until the morning of the following day; and the resulting factors, which were the mortality within 30 days of the operation and the postoperative renal function.

The variables included in the analysis were either alternatives of the type 0 (= does not belong) or 1 (= belongs) to, let us say, a certain operation group or qualitative variables (continuous variables), for example, the preoperative heart volume, in which a measured value was inserted for each patient. The alternative variables also included variables that had more than one step, for example, the postoperative renal function, for which the patients were divided into three groups, denoted by the figures 1, 2 and 3. In the regression analysis the resulting variables - postoperative mortality and renal function - were dependent (y) variables or regressands and the rest were independent (x) variables or regressors. All the data collected were taken from case records or the statements of patients or were the results of routine examinations. In order not to burden the exposition unnecessarily, a detailed account of the different routine methods used at the hospital was not given, especially as in this type of analysis it does not matter, on the whole, how a variable comes into existence, provided that it is consistent and is correctly recorded for all patients. The effect of variations in individual variables (for example, through irregular error) is described below in the discussion of Ch. IV. As has already been pointed out, there are a number of defects as regards consistency in recording, as certain decisions had necessarily to be made before the analysis, for example the decision to combine the patients in different diagnosis and operation groups. As regards other individual variables, for example, operative complications, which were divided into groups (none, slight or moderate, serious), the assessment was made according to the result. Thus, in 2 cases the blood circulation stopped on account of technical errors while the perfusion was going on, in the first case for 4 minutes and in the second for 12 minutes. The first patient survived and the complication was therefore described as "slight to moderate", but the second patient died as a result of anoxic damage and was therefore assigned to the "serious complications" group. However, in most cases there was no difficulty in recording the variables consistently.

As far as possible, correctness of recording was ensured by various kinds of checks, such as double punching of the punched cards, print-outs and manual checking of data included in individual analyses, checking by means of check sums, etc. During the actual analyses the checking devices incorporated in the computer were responsible for the elimination of incorrect calculations. For each patient about 700 different data were recorded (not all of them were used in the present work), which means that nearly 400.000 figures were punched on cards. In spite of the checks, it is not out of the question that isolated incorrect recordings may have been made, although it can probably be safely stated that no recording errors of such magnitude as to influence the statistically highly significant results, remain. The statistical methods used are also described in Ch. III.

The first section of Ch. IV contains only an account of the first resulting factor - the mortality within 30 days of the operation (IV, A). Of the 191 patients included in the study, 49 died within this period (Table 6 A) and for these patients a summary of the causes of death is given in Table 6 B. Eleven patients died of sepsis; all of them had some form of prosthesis inserted in the heart. In the 56 cases in which no antibiotics were added in the oxygenator, 8 patients died of sepsis, while the corresponding figure when antibiotics were added was 3 out of 125. Ten patients died probably as a result of coronary-artery anomalies or coronary

sclerosis, giving rise to poor coronary perfusion during ECC. In 4 cases these diseases were not diagnosed before the operation. Six patients died as a result of technical complications; three of these had total blocks and all three received "pacemaker" treatment. The distribution of fatal cases has been given in Table 6 A, while the mean values and SDs of a selection of preoperative variables in the seven operation groups are shown in Tables 4 and 5 for all the patients. These latter tables thus give a certain idea of the "general degree of severity" in the material, within the framework imposed by the operation indications.

In Ch. IV, B, the result of a simple correlation analysis between the mortality and the preoperative factors is reported and in Ch. IV, C, an explanation is given as to why multiple regression analysis must yield a better result than these simple correlations.

Ch. IV, D, is an account of the preparatory analyses which proved to be necessary in order to elucidate how multiple regression analysis could best be applied to the present material. The course of the analysis in these preparatory investigations has been summarized in Fig. 1. The result showed that the final analysis (the performance and result of which are reported in Ch. IV, D, 2) should be performed at a reduction criterion (p-level) adjusted so that only regressors whose coefficients achieved a significance level of at least(*) ($P \leq 0.05$) remained at the end of the analysis. Since the final selection of preoperative regressors was made from about 150 linear, squared or interaction variables, the final analysis was performed in a further two steps, with the reduction criterion adjusted so that only regression coefficients with significance levels of (**) and(***) remained after the reduced regression ($P \leq 0.01$ and 0.001 respectively). In this way the number of final regressors which remained by chance could be greatly reduced or completely eliminated. However, this was accompanied by a weakening of the correlation between the remaining combination of regressors and y, i.e. that part of the agreement between the predicted and the observed mortality which could be explained by the remaining regressors (R^2 was reduced from 0.569 at a p-level of 0.950 to 0.181 at a p-level of 0.999). Moreover the best explanatory value (maximum R^2, minimum residual variance) was obtained at a p-level of 0.80 but at this reduction criterion there still remained too many regressors (51), of which almost half could have remained by chance.

The regressors remaining after the final analysis at a p-level of 0.95 (31) have been shown in Table 9. Some of these regressors are representatives of other and more essential regressors, which were either not included in the analyses or were eliminated during the analyses, and some may have remained by chance, for which reasons the absolute medical significance of most individual regressors cannot be evaluated. On the other hand, a good prediction of the death risk within 30 days of the operation is obtained for the patients included in the material (corresponding to the value of R^2 obtained). In the hope that the operation risk for patients other than those included in the material could also be predicted with the aid of the final regressors obtained, these regressors were interpreted (Ch. IV, D, 3). The result of this interpretation was made the basis of a forecast index, which is summarized in Table 12. As the predictions outside the material were not satisfactory, attempts were made to produce by other means a forecast index which would function just as well in making predictions for the 74 patients outside the material as for the patients included in the material. In the best of these attempts there were selected for each operation group preoperative variables that had either a high simple correlation with y or a highly significant correlation with y after multiple regression analysis. This forecast index is presented in Table 13. It can be used - at least as regards patients with aortic-valve disease -

for predicting the death risk, for matching patients in experiments and the testing of drugs and, above all, as a basis of future expansion of the material through further annual analyses, taking into account the possible changes made in the technique and the indications.

In Ch. IV, D, 4, the prediction obtained within the material on the basis of preoperative status is examined and commented on. No patient who survived had had a predicted death risk of over 60 % and only 9 of those who died had had a predicted death risk of under 40 %. Thus, the operation risk could be assessed preoperatively with very satisfactory precision. In this connection the causes of death of patients with low predicted values were examined and, in doing so, it emerged that the prediction could be further improved if the coronary arteries were mapped carefully before the operation and if the frequency of sepsis could be reduced.

In Ch. IV, E, are discussed the defects in the form of regression analysis and the results of the attempts made to apply the method to the correlation of the preoperative factors with the mortality within 30 days of the operation in the patient material previously reported.

By way of summary, it may be said that the method affords great possibilities of forecasting the death risk for individual patients, of isolating the significance of individual factors and of making comparisons in different respects between patients (or patient groups) with different preoperative status. Of the attempts that have been made to apply the method to the material reported, with the mortality as the resulting factor, it may be said that they were largely unsuccessful, primarily because the number of patients was too small. In the largest operation group (group I), consisting of 96 patients, in which repairs were carried out on morbid changes in or near the aortic ostium, a better result could be achieved than in other groups in which the number of patients was much lower. As has already been reported, it is implicit in the method that regressors which at different values have sufficiently large differences in the percentages of dead and living patients and at the same time sufficiently large regression coefficients in relation to the variations within the regressor will finally determine the correlation between the observed and the predicted mortality. The larger the material and the smaller the irregular error, the greater the chance a regression coefficient has of asserting itself at a significant level in the analysis. An example is operation group VI (correction of Fallot´s tetralogy), which consisted of 18 patients, 4 of whom died within 30 days of the operation. In these 4 fatal cases, 3 patients had high Hb values (about 23 g%), while the fourth had a lower one (15 g%). As the survivors had, on the average, lower Hb values than the dead patients, this regressor achieved a significant level (***) in the final analysis. A high Hb value in patients with Fallot´s tetralogy is a symptom of the degree of cyanosis and thereby of the size of the shunt and this in its turn is a sign of the anatomical character of the defect. The significant correlation between high Hb levels preoperatively and the mortality therefore appears logical from the medical point of view. However, the significance of this regressor would have been quite different if, for example, a further 2 patients with low Hb values had happened to die of operative complications, which had no connection with the preoperative status. In that case the regressor would probably not have reached a significant level.

The example quoted shows how difficult and uncertain it is to generalize the significance of individual regressors obtained from an analysis of so relatively small a material as that used here. As, in addition, a number of final regressors may have remained by chance and others were more or less easily interpreted representatives of background factors, only a few of the results obtained can be considered to have general validity. Thus, in all the analyses performed the preopera-

tive heart volume proved to be the most important individual factor for aortic defects and combined aortic- and mitral-valve defects, with an increase of the risk in aortic-valve operations of 20 % when the heart volume was 1000 ml/m^2 instead of 500 ml/m^2. In cases of mitral-valve defects and shunt cases, a large heart volume only involved a small increase in the operation risk. An acquired defect involved a considerably greater risk than a congenital defect. In the group of aortic operations, other concurrent defects and an increased end-diastolic pressure in the LV also increased the risk, and stenosis involved a considerably greater risk than insufficiency.

An analysis of the effect of irregular error on the regression coefficients showed that these coefficients were substantially increased if the presumptive error was deducted. This means that a number of variables which now appear to be insignificant may do so because the variations within the variable are too large. If irregular and systematic errors could be avoided, the regression coefficients that are now significant would probably be further increased, regressors that are now eliminated would reach their true level of significance, even in the analysis of relatively small materials.

In Ch. V the mutual importance of pre- and peroperative factors was analysed, and it emerged that preoperative factors mainly explained the mortality. While the peroperative factors certainly made a significant contribution to the mortality, this contribution was much less than that of the preoperative factors. An analysis of the correlation between the remaining peroperative regressors with a (***) level of significance and a selection of representative preoperative variables showed that changes in weight during the operation and the length of the operation period were largely explained by preoperative factors, while re-operation on account of hemorrhage and the duration of falls in blood pressure during ECC certainly had a significant connection with isolated preoperative factors but mainly exerted an effect on the mortality by themselves. A large supply of K^+ during the operation day significantly reduced the mortality.

In Ch. VI the method (multiple regression analysis) was applied to the material, with the postoperative renal function as a resulting variable. It was possible to avoid paradoxical coefficient values among the regressors which reached a high level of significance, probably owing to the fact that the dependent variable now contained three groups as against two for the mortality within 30 days. The division of the material into three groups with different postoperative renal functions is explained and discussed in the introduction to the chapter, which also includes an account of the different steps in the analysis. It was clear from the analyses made in connection with this division that patients who after the operation had a NPN value of over 40 mg% for at most 24 hours (renal-function group 1) displayed significantly higher values (***) than the others for creatinine clearance and urine/blood ratios of creatinine and urea during the operation day, after the conclusion of the operation and during the first 2 days after the operation. However, there was a statistical difference (***) between groups 1 and 3 even during the three measuring periods in the course of the operation, as regarded creatinine clearance, which thus proved to be the earliest of the prognostic signs of postoperative renal damage examined here.* Of the 92 patients in group 1, 5 (5.4 %) died within 30 days of the operation; of the 74 in group 2, 20 (27 %) died and all the 15 patients with acute renal failure died within 5 weeks. However, this increase in mortality cannot be ascribed to the increased element of postoperative renal damage, since (among the fatal cases) this damage did not appear in isolation but was preceded by or combined with other postoperative complications. At the autopsies signs of renal da-

*The concentrations in urine of creatinine and urea, for the periods during the day of operation, were compared with the respective serum levels on the next morning.

mage which had been present before the operation could be observed only in a small number of cases.

The results of the regression analyses have been reported and interpreted in Ch. VI, B, and discussed in Ch. VI, C. In this connection it appeared that, as in the case of the mortality rate, the relative heart volume was the most important single preoperative factor and that the preoperative creatinine clearance is an important factor in the prognosis. Of the important peroperative variables, the quantity of urine excreted during the operation day may be mentioned; primes or other measures which produce a high rate of diuresis seem to afford a significant protection against renal damage.

A comparison with a fairly similar material found in the literature (Yeh et al. 1964) showed that the five peroperative factors which proved in their material to give rise to a significantly reduced postoperative renal function were not significant in the present material, probably because considerably more peroperative variables and also preoperative variables were taken into account simultaneously. In the regression analysis in the present work one factor - the length of the perfusion time - had a probably significant real correlation with the postoperative renal function. The reasonable assumption that defects whose repair necessarily requires a long perfusion time for that reason alone produce a worse postoperative renal function than others has not proved to apply to the material analysed here.

A comparison with another very large but dissimilar material (Doberneck et al. 1962) showed greater agreement with the present material, especially as regarded the influence of background factors and such intermediate regressors as proved to have stable coefficients at different stages of the analysis.

This shows that it is possible to assess, with relatively satisfactory reliability, the influence on the postoperative renal function of underlying factors in the causal chain by percentual calculations, simple correlation or single factor analysis. As regards the intermediate factors in the chain, such as the peroperative factors, multiple regression analysis must be performed and the results interpreted, for here the simple correlations yield incorrect results, unless a very stable factor of the "operative complications" type (only slightly correlated with other factors) is involved. As analyses that are methodologically comparable with the present investigation have not been found in the literature concerning open-heart surgery, no further comparisons have been made with other materials. On the other hand, there is a discussion, against the background provided by a summary of recent experience of acute renal failure made by Parry (1965), of the possibilities of explaining the fact that the quantity of urine excreted during the operation day proved to be the most interesting factor in this investigation, as regarded an improved postoperative renal function.

However, similar investigations have been published in other spheres of surgery and therefore it may, in conclusion, be of interest to try to illustrate in which spheres of clinical research (or "production control") multiple regression analysis may be of value. Certain conditions must, of course, be fulfilled; there must be opportunities of collaborating with experts in medical statistics and a sufficiently large computer must be available. It must also be assumed that innumerable problems of recording and identification have been solved. It is probably of small importance whether one then (as in the present work) reduces the number of recorded independent variables taken from a large primary pool or arranges them in a causal chain, which is processed from the background up to the resulting variable. If the material is sufficiently large, one gets as a result (according to the reduction criterion chosen) a combination of regressors that will have a higher significant correlation with the dependent variable than will the deleted

variables.

In clinical research a large number of investigations are designed to determine whether a certain type of treatment is better than others and, as a sub-division of this question, why certain individuals fare better than others who have been treated in exactly the same way. The first part of this question might no doubt be answered best if in prospective investigations the material was selected at random and all the treatment variables were kept constant. On account of individual differences in the patients, which sometimes necessitate departures from this principle, and of preconceived ideas as to what is adequate therapy and best for the patient´s welfare, extremely few investigations have been carried out consistently in this way. As multiple regression analysis provides very good opportunities of comparison, while taking account of background factors, even in retrospective investigations, it would seem to be capable of playing a great part in this connection.

As regards the other question - why certain individuals fare better than others after the same treatment - it is likely in future to play a quite predominant part. As gradually the patient records from hospitals are filed in such a form (for example, on magnetic tape) that they can be rapidly processed by computer, this matter (for example, all follow-up examinations) will probably be transferred from "research" to "production control".* By multiple regression analysis it is possible to check annually the results of the work done, to compare different methods of treatment, to assess the value of newly introduced methods of investigation and the validity of diagnosis groups etc. On the basis of these annual analyses, it is also possible to obtain simple prediction summaries for individual patients or groups of patients. Such a forecast index may refer to any resulting variable whatever and may illustrate, for example, the operation risk, the risk of thrombo-embolism, postoperative hemorrhage, etc., against the background of the pre- and/or peroperative factors for an individual patient or collectively for groups of patients. Annual checks of the material by multiple regression analysis also have the advantage that no recorded variable can be forgotten, as each time it has an opportunity of asserting itself.

*This is not, of course, inconsistent with the self-evident fact that the biological effect of the individual variable must always, as far as possible, be made clear by separate basic studies.

CONCLUSIONS

1. MORTALITY WITHIN 30 DAYS OF THE OPERATION

(a) Multiple regression analysis can be used successfully to find out whether the preoperative status of different groups of patients is equivalent, provided that the patient material is sufficiently large. In this way it is possible to take into account the preoperative status in planning experiments, testing drugs and making comparisons within and between different clinics, in which case a simple forecast index, based on the analyses, should be prepared.

(b) By multiple regression analysis the mutual importance of isolated factors or groups of factors for a selected resulting variable can be discovered, provided that the material is so large that the random errors are not predominant.

(c) The material analysed in this work was too small to provide reliable results in accordance with (a), though it was large enough to facilitate the design of a forecast index which, even in its present form, gives a relatively reliable prediction of the operation risk, at any rate for the planned aortic-valve operations, both within and outside the material. Moreover, with a relatively small amount of programming work and computer time, this forecast index can be extended by annual analyses.

(d) The material was also too small to yield more than a few significant answers in accordance with (b) - answers which may conceivably have a general validity. However, it was clear that the mortality within 30 days of the operation was more dependent on the patient´s preoperative status than on the choice of anesthesia, the use of a bubble or a disc oxygenator and the choice of prime. However, complications during the operation, long operation times and long durations of falls in blood pressure (< 80 mmHg) during ECC increase the mortality significantly, while an increased supply of K^+ and a high rate of diuresis during the operation day reduce it significantly. As regarded the preoperative factors, patients with acquired defects had a considerably higher mortality than patients with congenital defects, as was expected, while the individual factor that was of greatest importance proved to be the preoperative heart volume in fatal cases following operations for aortic-valve defects and combined operations on aortic- and mitral-valve defects. A high end-diastolic pressure in the LV in cases of aortic-valve defects and a high Hb in cases of Fallot´s tetralogy led to unfavorable prognoses.

2. THE POSTOPERATIVE RENAL FUNCTION IN THIS MATERIAL

(a) If the material is divided into three groups (no clinically demonstrable postoperative restriction of the renal function (group 1), clinically demonstrable restriction of renal function (group 2), and acute renal failure (group 3)) and the only difference between groups 1 and 2 is that the patients in the latter group have a NPN increase of over 40 mg% for at least 2 days after the operation, the present analyses indicate that the cases in group 2 are, on the average, nearer group 3 than group 1, in spite of the fact that a number of borderline cases (in group 1) should no doubt really have belonged to group 2 and vice versa.

(b) The earliest and best prognostic symptom of impending acute renal failure is the creatinine clearance, while the ratios of urea and/or creatinine in the urine and blood are of value in the prognosis only after the operation has been concluded.*

(c) The mortality increases greatly with an increasing degree of postoperative restriction in the renal function, probably not on account of this restriction but rather because the renal damage is also a sequela of complications which later cause death.

(d) Previous kidney disease is an insignificant factor among those which cause postoperative renal damage in patients chosen for open-heart surgery according to the indications listed in Ch. II.

(e) Preoperative factors are of relatively less significance and peroperative factors of more significance for the postoperative renal function than for the mortality.

(f) As in the case of the mortality, the heart volume is the most important individual variable amongst the preoperative factors for acquired defects, except mitral-valve defects. Acquired defects carry a greater risk of postoperative renal damage than congenital defects. As regards the congenital defects, patients with Fallot's tetralogy are at greater risk than other patients and as regards aortic-valve defects, stenosis carries a considerably greater risk than aortic insufficiency.

(g) Of the peroperative factors, a long perfusion time, a low esophagus temperature during total perfusion and a small quantity of urine excreted during the operation day involve a significantly greater degree of postoperative restriction in the renal function.

(h) The choice of anesthetic, the choice of bubble or disc oxygenator, the degree of hemolysis, the blood flow achieved during perfusion, the duration of coronary perfusion in relation to the period of aortic shut-down and the effect of the operation performed had in themselves no significant correlations with the postoperative renal function in the present material, probably because their effect was better expressed by other regressors.

(i) Of the primes used in this material, blood + mannitol and blood + mannitol + Rheomacrodex proved to be the best. However, there were no significant differences as between the primes. It seems as if primes that produce a large volume of urine are to be preferred from the viewpoint of renal function. The addition of mannitol to the prime consisting of blood + Rheomacrodex resulted in this prime proving to be the best, although it was previously one of the worst from the viewpoint of renal function.

(j) In this material a large volume of urine during the operation day was statistically highly correlated with improved postoperative renal function. Patients who are to be operated on should not be restricted as regards their fluid intake before the operation. Primes which produce a high rate of diuresis should be used, the urine production should be continuously watched during the operation day and therapy directed against oliguria should be initiated at once, possibly in the form of osmotic diuresis.

(k) The above conclusions are based on the present material but have probably general validity.

* When measured as described on p. 59.

3. SOME STATISTICAL AND CLINICAL ASPECTS

(a) Developments in open-heart surgery are proceeding so rapidly and the differences in technique, indications, etc. as between different clinics are so great that large materials, which can give really general validity to the results of inquiries of this type, can only be investigated at a few departments of cardiac surgery. Under Swedish conditions the material must be increased by annual analyses or by collaboration between different clinics.

(b) As is clear from the above remarks, the method described here could yield considerably more reliable results if it were applied in other spheres of medicine than open-heart surgery (though it is needed there for the same reasons), as it is so far the only fairly reliable method of taking into account other factors than those that are of immediate interest. The analysis of single factors, for example, by simple correlation analysis, has often proved to be quite inadequate in comparison with multiple regression analysis. The results of clinical investigations should therefore preferably be evaluated by the latter method in future, in view of the lack of published reports of homogeneous and randomized experiments.

APPENDIX I

FIGURES AND TABLES

Fig. 1. Steps in trial analysis of preoperative data

Step 1 — 191 patients

74 preoperative x-variables were analysed at:

(a) p-level 0.05: 74 regressors not deleted,
(b) p-level 0.70: 36 regressors not deleted,
(c) p-level 0.95: 15 regressors not deleted.

Step 2 — 181 patients

74 preoperative x-variables were analysed at:
p-level 0.70: 38 regressors were not deleted.

Step 3 — 191 patients

80 preoperative x-variables were analysed at:

(a) p-level 0.95: 16 regressors were not deleted.
(b) The 16 regressors from (a) were analysed together with the interaction variables of these 16 and operation groups I-VI, a total of 80 regressors at a p-level of 0.95: 26 regressors were not deleted.

Step 4 — 181 patients

The 26 remaining regressors from 3 (b) were analysed for 181 patients at p-levle 0.00, thus no regressor was deleted.

Step 5 — 191 patients

The 26 remaining regressors from 3 (b) were analysed at p-level 0.00: the patients with absurd predicted values were given a weighting of 9 and other patients a weighting of 1.

Step 6 — 191 patients

The remaining regressors from 3 (b) plus 36 re-inserted (in step 3 (a) and (b) deleted) preoperative variables were analysed at p-level 0.00

(a) with weighting 1 for all patients,
(b) with weighting 9 for patients with absurd predicted values.

This figure refers to text in Ch. IV, D. (beginning on p. 31).

Fig. 2. Predicted values derived from preoperative variables and pre- and peroperative variables.

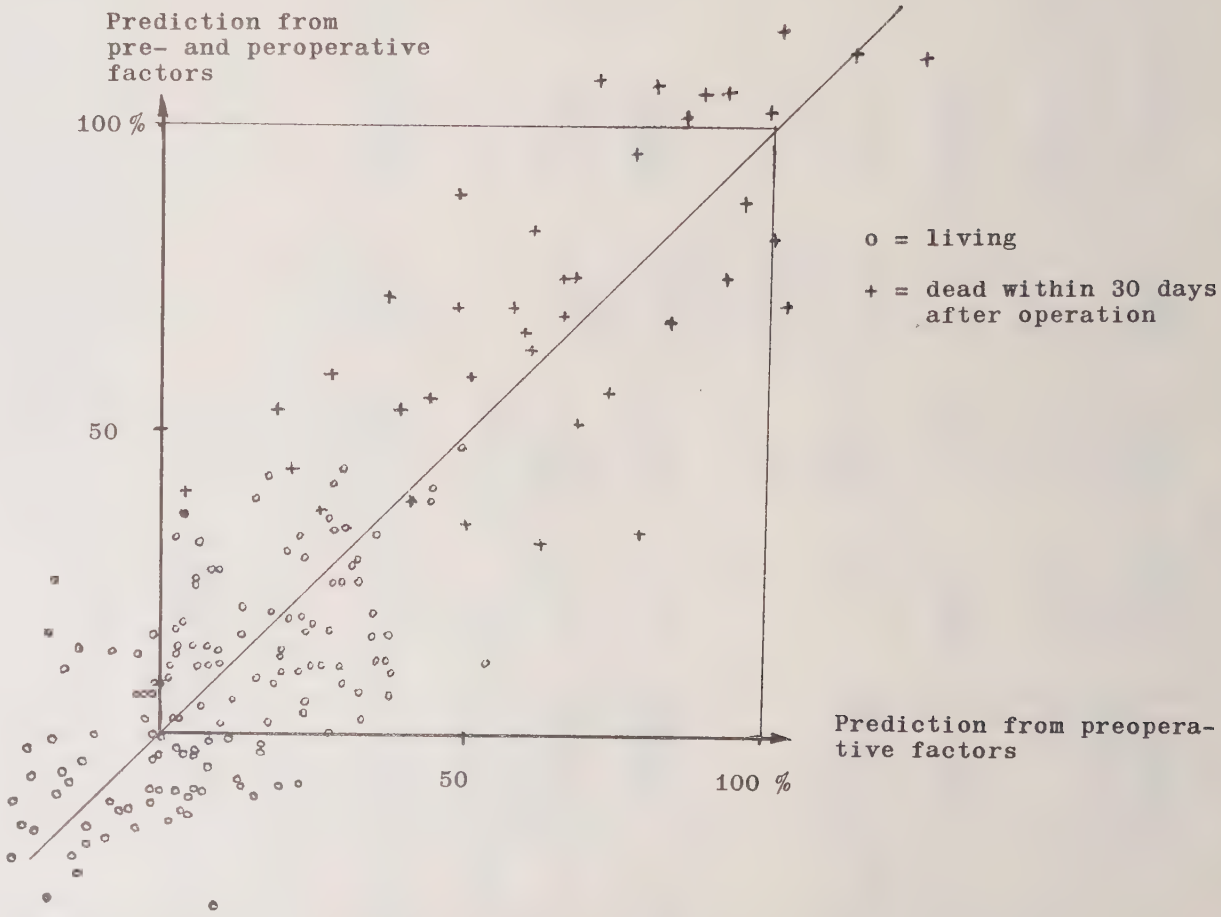


Fig. 2 refers to text in Ch. V.

Table 1. Examples of mortality rates in various materials

Authors	Age of patients (range)	Time of observation	Perfusion time (minutes)	Hypothermia (°C)	Flow rate
Cooley et al. 1962	?	?	?	?	80 ml/kg/min
Riker et al. 1962	0.5-17 years	2 - 4 years	?	34-36°	2.0 l/m^2 BSA/min
Neptune & Bougas 1962	Children to > 60 years	?	Mean 60-90 for acquired	Not < 20°	?
Zudhi et al. 1964	Children -adults	4 mo.	Mean ca 60	28-30°	< 20 ml kg/min
Norman et al. 1964	Children -adults	2 mo.	Mean ca 80	30°	60/80 ml/kg/min
Grismer et al. 1964	16-61 years	1 mo.	106-330	?	?
Starr et al. 1964	24-54 years	1 - 15 mo.	Mean 190 for surviving patients	30°	1.8 l/m^2 /min
Kirklin 1964	Adults	1 - 15 mo.	?	?	?
McGoon et al. 1964	Children - adults	Time of hospitalization	?	?	?

Notes on Table 1. (see text on p. 9)

The mortality in each material is first given in absolute figures (2/16) and then as a percentage (12.5 %). D/W = dextrose in water.
Of the patients classified as "multiple lesions" those reported in the last four papers were operated upon for two or more lesions.

Perfusion pressure	Type of oxygen. used	Prime	Mortality rate in different heart lesions: Congenital Fallot	Congenital Other	Acquired One lesion	Acquired Multiple lesions
50-80 mm Hg	Bubble	20 ml/kg 5 % D/W	2/16= 12.5%	4/61= 6.6%	8/23= 34.8%	-
?	Disc	Blood	15/60= 25%	12/140= 8.6%	-	-
?	Bubble	100 ml 0.9 % NaCl and 1000 ml Rheomacr. + possibly 500 ACD blood	-	0/8= 0%	8/67= 12%	18/30= 60%
?	Bubble	16 ml/kg 5% D/W or blood	6/15= 40%	13/149= 8.7%	17/86= 19.8%	-
?	Disc	Blood	5/57= 8.8%	10/184= 0.5%	16/94= 17%	12/25= 48%
?	Bubble	?	-	-	12/26= 46%	6/6= 100%
> 65 mm Hg	Disc	Blood + mannitol 2 g/kg b.w.	-	-	-	7/40= 17.5%
?	?	?	-	-	-	4/25= 16%
?	?	?	19/116= 16.4%	17/338= 5.0%	33/200= 16.5%	9/44= 20.5%

In some of the papers "one lesion" means "predominant lesion". In the last two papers the technic of perfusion is that employed by Kirklin and his group.
The material of McGoon et al. includes 46 patients with miscellaneous congenital and acquired lesion which could not be included in the table.

Table 2 A. Distribution of the material according to diagnosis

(One patient can belong to more than one group)

Diagnosis in "single" lesions	No. of cases	Belongs to diagnostic group no.
A I	32	
A I + A S	35	
A I + Sub A S	1	
A I + Valsalva aneurysm or aneurysm aorta ascendens	3	I (85 cases)
A S	9	
Sub A S	4	
A S congenita + Sub A S	1	
M I	8	
M S	1	
M I + M S	12	II (22 cases)
Ruptura valv.tricuspid. traumatica	1	
ASD sec.	8	
VSD	7	
AV com.	4	III (20 cases)
ASD sec. + P S	1	
Fallot´s tetralogy	18	IV (18 cases)
Aneurysm, right ventricle	1	
Aneurysm, left ventricle	4	
Aneurysm, aorta	3	V (14 cases)
Tumor cordis	4	
Infundibular stricture + P S	1	
Angina pectoris	1	

Table 2 B. Patients with "combined" lesions

	A I	A I + A S	ASD prim.	ASD sec.
M I	10	2	3	-
M S	2	3	-	-
M I + M S	3	2	-	-
M I + M S + T I	1	-	-	-
VSD	4	1	-	-
T I	-	-	-	1

Total in diagnostic groups I + II = 23 cases
I + III = 5 cases
II + III = 3 cases

A I = Aortic valve insufficiency
A S = Aortic valve stenosis
Sub A S = Subaortic stenosis
M I = Mitral valve insufficiency
M S = Mitral valve stenosis
ASD sec. = Atrial septal defect of secundum type
ASD prim. = Atrial septal defect of primum type
VSD = Ventricular septal defect
AV com. = Common atrio-ventricular canal
P S = Pulmonary valvular stenosis
T I = Tricuspid valvular unsufficiency
I S = Infundibular stenosis
Ao = Aorta

Table 2 refers to text in Ch. II, A and D (pp. 11-12 and 15).

Table 3. Distribution of the material according to type of operation

(One patient can only belong to one group)

					Oxygenator		
A. Operation group I, (aortic operations)	B	B+R	B+M	"Mixed"	Tot. disc.	Tot. bubble	Total
Starr prosthesis in aorta	21	14	12	8	55	19	74
Starr prosthesis in aorta + aortic prosthesis	1	0	0	0	1	1	2
Starr prosthesis + suture of VSD	0	0	0	3	3	0	3
Starr prosthesis + res. of I S	0	0	0	1	1	0	1
Suture of insuff. besides Starr prosthesis	1	1	0	1	3	0	3
Pericardial prosthesis in aorta	1	0	0	0	1	0	1
Pericardial prosthesis in aorta + suture of VSD	0	0	1	0	1	0	1
Commissurotomy of congen. A S	0	0	0	0	0	5	5
Res. of infundibular stricture or muscle hypertrophy	1	1	1	0	3	2	5
Plastic procedure on cusp	1	0	0	0	1	0	1
Total	26	16	14	13	69	27	96

80 Starr prostheses in aorta + suture of insuff. besides 3 earlier inserted
2 pericardial prostheses

B. Operation group II + IV. (mitral operations)							
Annuloplasty	0	1	2	0	3	1	4
Plication of mitral cusp	0	1	0	0	1	0	1
Annuloplasty + plication	0	1	1	0	2	1	3
Starr prosthesis in mitral valve	4	5	2	1	12	6	18
Starr prosthesis in tricuspid valve	0	0	1	0	1	1	2
Total	4	8	6	1	19	9	28

8 plastic procedures
20 Starr prostheses

C. Operation group III. (combined aortic-mitral procedures)							
Starr in aorta + dil. or annuloplasty in mitral or Starr prosthesis in both aorta and mitral ostia	3	4	1	2	10	2	12
Total							

12 combined procedures

					Oxygenator		
D. Operation group V. (Shunts, not Fallot's tetralogy)	B	B+R	B+M	"Mixed"	Tot. disc.	Tot. bubble	Total
Direct suture	2	3	1	0	6	6	12
Patch graft	0	1	1	0	2	2	4
Mitral cusp suture + patch graft in ASD prim. or AV-com.	0	1	0	1	2	4	6
Direct suture of ASD sec. + opening P S	0	0	0	0	0	1	1
Total	2	5	2	1	10	13	23
13 direct sutures 10 patch grafts							
E. Operation group VI. (Fallot's tetralogy)							
Total correction of Fallot's tetralogy	3	4	1	1	9	3	12
Total correction of Fallot's tetralogy + closure of Blalock shunt	1	2	2	0	5	1	6
Total	4	6	3	1	14	4	18
12 total corrections 6 total corrections + closure of Blalock shunts							
F. Operation group VII. (Miscellaneous procedures)							
Res.+graft of aortic aneurysm	0	2	1	0	3	0	3
Exc. of tumor cordis	1	0	1	0	2	2	4
Exc. of ventricular aneurysm	1	1	2	0	4	1	5
Thrombendarterectomy + graft in left coronary artery	0	1	0	0	1	0	1
Com.tomy of PS + Res. IS in RV	0	0	0	0	0	1	1
Total	2	4	4	0	10	4	14
13 miscellaneous procedures							

B, B+R, B+M and "Mixed" denotes primes used in the disc oxygenator.

For explanation, see text, p. 12.

— Table 4. Mean values and SE of some preoperative factors. Distribution according to operation group.

Op. group no.	No. of pat.	Sex ♂	Sex ♀	Age	Type of lesion Acq.	Type of lesion Cong.	Heart volume	Syst. BP	Diast.BP	Preop. urine	Weight	Hb
I	96	77	19	39.0±1.2	81	15	679± 19	142 ±2.7	69 ±2.1	1192± 35	67.5±1.3	13.4±0.15
II	8	2	6	37.0±4.1	8	0	800± 74	140.0±5.8	87 ±2.5	1316±143	64.2±5.0	12.6±0.48
III	12	7	5	36.5±2.0	12	0	783± 40	140.8±5.7	65.8±5.8	1210± 64	64.9±2.1	13.0±0.42
IV	20	12	8	41.4±2.1	19	1	921±103	137.5±3.7	86.8±3.0	1316± 70	64.9±2.6	14.0±0.36
V	23	9	14	32.5±2.5	0	23	744±108	132.1±2.2	79.8±2.5	1199± 51	61.7±2.8	13.4±0.34
VI	18	13	5	30.3±3.5	0	18	520± 31	131.3±3.8	83.8±1.8	1085± 69	57.2±2.3	17.1±0.82
VII	14	12	2	48.5±4.4	12	2	607± 50	140.0±6.3	89.2±3.7	1154± 68	64.2±3.4	13.2±0.35

	Cl^- in serum	HCO_3^- in venous blood	NPN	Creatinine	Duration of disease	Duration of symptoms	Inability to work	Duration of atrial fibrillation
I	103.0±0.40	22.6±0.22	32.0±0.51	0.98±0.019	19.2±1.45	6.2±0.89	0.49±0.12	0.04±0.02
II	100.9±1.49	23.1±0.62	30.4±1.39	0.83±0.105	18.9±4.63	10.4±4.54	0.28±0.25	1.75±0.25
III	100.4±1.25	22.5±0.64	30.0±1.21	1.03±0.072	19.2±2.98	10.5±3.09	0.78±0.33	2.58±0.84
IV	102.4±1.03	22.3±0.42	31.0±0.64	1.02±0.037	17.1±2.80	5.6±0.87	0.68±0.22	3.35±0.67
V	104.6±0.85	21.5±0.35	29.7±0.71	0.96±0.050	27.1±3.21	8.9±2.19	1.42±1.16	0.04±0.04
VI	107.2±1.23	20.5±0.47	33.8±1.01	1.06±0.065	27.1±3.86	18.9±3.61	2.33±1.68	0
VII	99.4±1.30	23.1±0.44	33.3±1.67	0.99±0.024	3.0±0.43	2.7±0.52	1.08±0.23	0

(Table 4 continues on next page)

Op. group no.	Hemato-crit	Serum protein	Na^+ in serum	K^+ in serum	Duration of digitalis treatment	No. of embolic episodes	Syst. PA at rest	"Preop. insuff."	Preop. creat. cl.
I	41.5±0.43	7.04±0.05	140.7±0.38	4.09±0.05	1.8 ±0.42	0.03±0.02	30.5±1.6	27-39-29	107.8±2.0
II	40.1±1.84	7.35±0.18	137.0±1.31	4.06±0.16	3.96±2.24	0	35.0±8.4	1- 3- 4	112.3±5.4
III	41.5±1.29	7.38±0.16	141.0±1.07	4.33±0.18	4.54±1.28	0.42±0.26	46.8±4.2	0- 4- 8	97.9±7.5
IV	43.1±0.95	7.21±0.12	138.7±0.90	4.17±0.07	3.75±0.62	0.20±0.09	32.2±2.7	2- 5-13	92.0±5.9
V	41.8±0.97	7.28±0.08	139.4±0.77	4.10±0.06	1.98±1.03	0	34.2±3.7	17- 5- 3	98.7±5.3
VI	56.1±0.30	7.35±0.13	140.0±0.93	4.23±0.11	0.65±0.28	0	20.7±2.5	12- 5- 1	101.1±7.5
VII	41.8±1.21	7.02±0.20	139.3±2.12	4.11±0.08	0.24±0.17	0.15±0.10	14.6±6.1	6- 2- 5	94.2±7.9

	Work-load test	PCV at rest	Aortic gradient	Degree of aortic in-sufficiency	Degree of mitral in-sufficiency	Syst. RV pressure	Pulmona-ry gra-dient	Systemic blood flow	O_2-satura-tion in ar-terial blood	Shunt in l/min
I	568±27	11.1±0.6	34.4±4.5	3.09±0.14	-	-	-	5.7±1.4	-	-
II	406±57	13.8±3.4	-	-	3.75±0.16	-	-	5.2±0.7	-	-
III	417±44	23.3±2.5	9.6±4.3	3.92±0.08	1.72±0.18	-	-	4.8±0.5	-	-
IV	415±50	15.2±1.7	-	-	3.28±0.08	-	-	4.0±2.1	-	-
V	554±36	7.5±0.8	-	-	-	-	-	4.5±1.4	-	8.7±1.3
VI	398±45	-	-	-	-	106.2±6.8	87.8±8.4	-	75.1±6.3	-
VII	435±46	-	-	-	-	-	-	-	-	-

Notes on Table 4 (see text p. 29)

In this table the means (and the SEs of means) of a selection of preoperative data have been brought together for the different groups of operations.
"Preoperative insufficiency" has been evaluated as 1,2 or 3, where 1 = no preoperative medication with digitalis or diuretics, 2 = medication with digitalis, and 3 = medication with both. The number of patients in the groups of operations have been divided into these three classes, for example, in group I: 27 - 39 - 29.
For the degree of insufficiency in the aortic or mitral valves, the means and the distribution of the grading 0 - 4 have been introduced. The units for other mean values in this table are not specified, but are those elsewhere used in this work according to the usual convention. Thus pressures are expressed in mm Hg, heart volume in ml/m^2 BSA, duration of disease in years etc.

Table 5. Distribution of LV and RV hypertrophy and other ECG changes in the operation groups. 1 = no changes, 2 = moderate and 3 = pronounced changes.

Operation group no.	LV hypertrophy			RV hypertrophy			"Other ECG changes"		
	1	2	3	1	2	3	1	2	3
I	15	33	48	96	0	1	62	15	19
II + IV	17	10	1	28	0	0	8	3	17
III	6	3	3	12	0	0	2	3	7
V	18	4	1	10	7	6	10	6	7
VI	18	0	0	2	1	15	15	2	1
VII	13	1	0	12	0	2	7	1	6

"Other ECG changes", group 2: AV block I - II; ST - T elevation; prolonged activation time; VES; atrial hypertrophy, abnormal T-wave.

"Other ECG changes", group 3: Bundle branch block; atrial fibrillation; myocardial infarction; more than two changes in group 2.

For definitions, see text, p. 19.

Table 6. 30-day mortality among 191 cases

A. Distribution according to operation group and time of death after operation.

Operation group no.	No. of patients	Nos. of deaths (mortality groups) Group 1	Group 2	Group 3	All	%
I	96	4	13	7	24	25.0
II	8	0	1	0	1	12.5
III	12	2	3	0	5	41.7
IV	20	2	2	0	4	20.0
V	23	0	3	0	3	13 0
VI	18	1	2	1	4	22.2
VII	14	1	7	0	8	57.1
Total	191	10	31	8	49	25.7

Mortality group 1 = dead within 24 hours.
2 = dead in 1-10 days.
3 = dead in 11-30 days.

Operation group I = predominant aortic lesions
II = predominant mitral lesions (no prosthesis inserted).
III = combined procedures on aortic and mitral lesions.
IV = predominant mitral lesions (Starr ball-valve).
V = shunts, (not Fallot).
VI = Fallot's tetralogy.
VII = miscellaneous operations.

B. Distribution according to cause of death.

Cause of death	Mortality group 1 Within 24 hours	2 1-10 days	3 11-30 days	Total no. of patients
Sepsis	0	7	4	11
Technical complications	3	0	0	3
Technical: Total block	0	2	1	3
Coronary anomaly and/or sclerosis	1	9	0	10
Ventilatory complication	0	1	0	1
Thrombosis on aortic prosthesis	0	0	1	1
Embolic episodes	0	2	0	2
Myocardial infarction	2	3	0	5
Acute renal failure	0	0	2	2
Anoxic brain damage	0	3	0	3
Subarachnoidal hemorrhage	1	0	0	1
Subdural hemorrhage	1	1	0	2
No obvious cause	2	3	0	5
Total	10	31	8	49

Table 6 refers to text in Ch. IV, A (pp 29-30).

Table 7. Regression coefficients, their SEs and significance levels (marked by asterisks) in the simple linear unreduced and reduced analysis of 74 x-variables at p-level 0.95 for 191 patients. y = mortality rate within 30 days postoperatively.

x-variable	★	Unreduced regression		Reduced regression p-level 0.95 (*)	
Heart volume (ml/m^2 BSA)	0.000250	0.000510	±0.000573	0.000474	±0.000116***
Operation group no. V	-0.157	-0.610	±0.516	-0.703	±0.227**
Operation group no. VI	-0.0379	-1.892	±1.354	-1.314	±0.448**
Operation group no. II + IV	-0.0914	-0.744	±0.318*	-0.608	±0.120***
Op.group I x Syst.pressure PA (mm Hg)	0.00217	0.0122	±0.0103	0.00537	±0.00249*
Op.group I x Aortic insufficiency	-0.00862	-0.0821	±0.176	0.138	±0.0289***
Op.group III x Aortic insufficiency	0.0458	-0.852	±0.826	-0.110	±0.0427**
Op.group V x Preop.flow (l/min)	-0.000518	0.00662	±0.00391	0.00821	±0.00257**
Op.group V x Shunt in l/min	-0.000655	-0.00570	±0.00350	-0.00700	±0.00263**
Congenital - Acquired lesion	0.0583	0.103	±0.104	0.143	±0.0365***
Only blood prime	-0.0542	-0.125	±0.262	-0.146	±0.0743*
Op.group I x Prime contains mannitol	-0.0542	-0.201	±0.345	-0.212	±0.0863*
Number of diagnosis	0.121	0.217	±0.106*	0.194	±0.0839*
Preop. K^+ in serum (mE/l).	-0.0108	-0.0101	±0.00883	-0.0182	±0.00680**
Op.group VI x Preop.(Hb g %)	0.000107	0.0117	±0.00473*	0.00815	±0.00248***

★ = Simple linear regression coefficient = $$\frac{\Sigma\,(x-\bar{x})\cdot(y-\bar{y})}{\Sigma\,(x-\bar{x})^2}$$

Table 7 refers to Fig. 1, step 1, (c), and text on pp. 31-32.

Table 8. Influence of different reduction criteria on the characteristics of three different analyses (degrees of freedom within brackets)

Sum of squares of deviations from the means.	Reduction criterion (p-level)		
	p = 0.05	p = 0.70	p = 0.95
Total	36.429 (190)	36.429 (190)	36.429 (190)
Due to regression	17.800 (71)	16.795 (36)	11.800 (15)
Due to error	18.630 (119)	19.634 (154)	24.629 (175)
Residual variance	0.157	0.127	0.141
Residual SD, (RSD)	0.396	0.357	0.375
R^2	0.489	0.461	0.324
Correlation coeff., R	0.699	0.679	0.569

Notes on Table 8

The sum of the squares due to error = the sum of the squares of the differences between the observed and predicted y-values.

Residual variance = the sum of the square due to error divided by the corresponding number of degrees of freedom.

RSD = $(\text{Residual variance})^{\frac{1}{2}}$

R^2 = the sum of the squares due to regression divided by the total sum of the squares.

Table 8 refers to Fig. 1, steps 1(a) - (c), and text on p. 32.

Table 9. Results of final analysis of preoperative factors. (y = 30-day mortality)

Remaining preoperative x-variables after final analysis	Step 1 (25 regressors). Remaining regressors after step 2.	Step 2 (31 regressors). Unreduced regression	Reduced regression
	Regression coefficients, their SEs and significance levels in 31 undeleted regressors		
1. Length-weight	$(1.22\pm0.41)10^{-1}$ **	$(1.31\pm0.46)10^{-1}$ **	$(1.36\pm0.39)10^{-1}$ ***
3. Belongs to more than one diagn.group	-1.684±0.508 **	-1.961±0.545 ***	-1.698±0.483 ***
6. Inability to work (years)	$(1.82\pm0.81)10^{-3}$ *	$(3.85\pm1.40)10^{-2}$ **	$(3.84\pm0.86)10^{-2}$ ***
9. HCO_3^- in venous blood (mE/l)	$(4.65\pm1.54)10^{-2}$ **	$(8.01\pm5.43)10^{-2}$	$(5.03\pm1.34)10^{-2}$ ***
11. Prime contains Rheomacrodex + mannitol	$-(2.20\pm0.78)10^{-1}$ **	$-(1.60\pm1.00)10^{-1}$	$-(1.78\pm0.61)10^{-1}$ **
16. Op. group III x flow (l/min)	$(1.94\pm0.71)10^{-2}$ **	$(1.37\pm3.63)10^{-1}$	$(2.43\pm0.69)10^{-2}$ ***
17. Op. group III x aortic gradient (mm Hg)	$(1.69\pm0.75)10^{-2}$ *	$(7.47\pm6.44)10^{-2}$	$(8.45\pm3.12)10^{-2}$ **
21. (Length-weight)^2	$-(5.98\pm1.93)10^{-4}$ **	$-(6.33\pm2.15)10^{-4}$ **	$-(6.64\pm1.82)10^{-4}$ ***
22. (Belongs to more than one diagn. group)^2	$(6.01\pm1.60)10^{-1}$ ***	$(5.96\pm1.75)10^{-1}$ ***	$(5.91\pm1.51)10^{-1}$ ***
23. (Heart volume)^2 (ml/m^2 BSA)	$(2.61\pm0.60)10^{-7}$ ***	$(1.58\pm0.51)10^{-6}$ **	$(1.11\pm0.24)10^{-6}$ ***
26. (Op. group I x end-diast. LV)^2		$(3.29\pm3.34)10^{-4}$	$(2.51\pm0.91)10^{-4}$ **
27. (Op. group I x degree of aortic insuff.)^2		$-(2.83\pm2.79)10^{-2}$	$-(3.91\pm0.68)10^{-2}$ ***
28. (Op. group II + IV x PCV at rest)^2(mm Hg)		$-(1.47\pm1.95)10^{-3}$	$-(1.45\pm0.55)10^{-3}$ **
29. (Op. group II + IV x syst. PA)^2(mm Hg)		$(4.98\pm4.23)10^{-4}$	$(3.48\pm0.96)10^{-4}$ ***
31. (Op. group III x aortic gradient)^2(mm Hg)		$-(2.11\pm1.29)10^{-3}$	$-(2.02\pm0.85)10^{-3}$ *
35. Op. group I x cong. or acq. lesion		$(4.14\pm3.20)10^{-1}$	$(3.49\pm0.70)10^{-1}$ ***
37. Op. group I x inability to work		$-(3.41\pm1.44)10^{-2}$ *	$-(3.23\pm0.92)10^{-2}$ ***
40. (Op. group I x heart volume)^2		$-(1.03\pm0.53)10^{-6}$	$-(6.28\pm2.73)10^{-7}$ *
43. Op. group II + IV x inability to work		$(4.26\pm3.38)10^{-2}$	$-(3.22\pm1.03)10^{-2}$ **
48. (Op. group II + IV x heart volume)^2		$-(1.32\pm0.52)10^{-6}$ **	$-(8.14\pm2.36)10^{-7}$ ***
51. Op. group III x inability to work		$-(7.50\pm4.75)10^{-2}$	$-(5.81\pm1.25)10^{-2}$ ***
52. Op. group III x Cl^- in serum (mE/l)		$-(2.75\pm6.37)10^{-2}$	$-(1.29\pm0.45)10^{-2}$ **
57. Op. group V x inability to work		$-(3.79\pm1.41)10^{-2}$ **	$-(3.79\pm0.87)10^{-2}$ ***
58. Op. group V x Cl^-		$(1.70\pm1.46)10^{-2}$	$(2.06\pm0.69)10^{-2}$ **
59. Op. group V x HCO_3^-		$-(6.39\pm6.43)10^{-2}$	$-(8.91\pm3.29)10^{-2}$ **
62. (Op. group V x heart volume)^2		$-(1.52\pm0.63)10^{-6}$ *	$-(1.07\pm0.36)10^{-6}$ **
64. (Op. group V x "other ECG changes")^2		$(7.26\pm3.83)10^{-2}$	$(4.92\pm2.06)10^{-2}$ *
65. Op. group VI x inability to work		$-(3.98\pm1.41)10^{-2}$ **	$-(3.70\pm0.87)10^{-2}$ ***
69. Op. group VI x pulm. gradient		$-(3.41\pm1.35)10^{-2}$ *	$-(6.08\pm3.09)10^{-3}$ *
71. (Op. group VI x heart volume)^2		$-(1.30\pm0.99)10^{-6}$	$-(1.44\pm0.61)10^{-6}$ *
79. Op. group VI x preop. Hb(g%)		$(1.97\pm0.67)10^{-1}$ **	$(7.62\pm1.67)10^{-2}$ ***

Table 9 refers to text on pp. 34-40.

1	3	6	9	11	16	17	21	22	23	26	27	28	29	31	35	37
	-ø	-ø	-.142*	ø	-ø	-ø	.997***	ø	ø	ø	-ø	ø	-ø	-ø	-.124	-ø
		-ø	.155*	.135	.487***	.280***	-ø	.987***	.156*	-ø	-ø	ø	ø	.248***	-.120	-ø
			ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-.103	.192**
				.148*	ø	-.113	-.138	.145*	ø	ø	.174*	ø	ø	-.130	.210**	ø
					-ø	-ø	ø	.123	-ø	ø	-ø	-.103	-ø	-ø	ø	ø
						.501***	-ø	.470***	ø	-.109	-.194**	-ø	-ø	.459***	.236**	-ø
							-ø	.270***	-ø	-ø	-.112	-ø	-ø	.980***	-.136	-ø
								ø	ø	ø	-ø	-ø	-ø	-ø	-.111	-ø
									.157*	-ø	-ø	ø	ø	.240***	-.107	-ø
										ø	ø	.357***	.194**	-ø	-ø	-ø
											.375***	-.117	-.110	-ø	.455***	.183*
												-.209**	-.197**	-ø	.859***	.311***
													.936***	-ø	-.254***	-ø
														-ø	-.240***	-ø
															-.120	-ø
																.322***

Table 10. Correlation coefficients between regressors listed in Table 9.

± ø = coefficient value lies between 0 and ± 0.10

40	43	48	51	52	57	58	59	62	64	65	69	71	79	x	x·y
-ø	ø	ø	-.111	-ø	-ø	ø	ø	ø	.106	ø	.185*	.145*	.246***	1	-ø
-ø	ø	.102	.289***	.512***	-ø	-ø	-ø	-ø	-ø	-ø	-.139	-.125	-.140	3	.117
-ø	ø	-ø	ø	-ø	.603***	ø	ø	ø	-ø	.737***	.178*	.267***	.211**	6	.115
.193**	ø	ø	.145*	ø	ø	-.153*	-.124	-.152*	-.129	-.102	-.299***	-.292***	-.315***	9	.138
ø	-ø	-ø	-ø	ø	-ø	.115	.103	ø	-ø	-ø	-ø	-.112	-ø	11	-.135
-.194**	-ø	-ø	.476***	.953***	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	16	.137
-.112	-ø	ø	ø	.555***	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	17	.100
-ø	ø	ø	-.105	-ø	-ø	ø	ø	ø	ø	ø	.183*	.142*	.246***	21	-ø
-ø	ø	ø	.280***	.494***	-ø	-ø	-ø	-ø	-ø	-ø	-.140	-.126	-.141	22	.123
.154*	.237**	.854***	ø	ø	-ø	-ø	-ø	ø	-ø	-ø	-.141	-ø	-.148*	23	.226**
.476***	-ø	-.111	-ø	-.114	-ø	-.171*	-.170*	-.148*	-.124	-ø	-.138	-.124	-.139	26	.173*
.776***	-.162*	-.199**	-.115	-.204**	-ø	-.306***	-.305***	-.265***	-.221**	-ø	-.247***	-.222**	-.248***	27	-ø
-.209**	.332***	.534***	-ø	-ø	-ø	-.103	-.103	-ø	-ø	-ø	-ø	-ø	-ø	28	ø
-.197**	.252***	.367***	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	29	ø
-ø	-ø	-ø	ø	.494***	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	31	ø
.815***	-.197**	-.242***	-.140	-.248***	-ø	-.372***	-.371***	-.322***	-.269***	-ø	-.300***	-.270***	-.302***	35	ø
.249***	-ø	-ø	-ø	-ø	-ø	-.115	-.115	-.100	-ø	-ø	-ø	-ø	-ø	37	.119
	-.162*	-.199**	-.115	-.204**	-ø	-.306***	-.305***	-.265***	-.222**	-ø	-.247***	-.222**	-.248***	40	.114
		.345***	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	43	-ø
			-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	48	ø
				.548***	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	-ø	51	-ø
					-ø	-.100	-.100	-ø	-ø	-ø	-ø	-ø	-ø	52	ø
						.233**	.265***	.172**	ø	-ø	-ø	-ø	-ø	57	-ø
							.994***	.864***	.719***	-ø	-.121	-.109	-.122	58	-.120
								.857***	.715***	-ø	-.121	-.109	-.122	59	-.127
									.752***	-ø	-.105	-ø	-.106	62	-ø
										-ø	-ø	-ø	-ø	64	ø
											.316***	.426***	.360***	65	.119
												.889***	.957***	69	-ø
													.866***	71	-ø
														79	ø

Table 10 refers to text on p. 34.

Table 11. Example of prediction of death risk

Values for a case in mortality group 1, inserted in 26 remaining regression coefficients in trial analysis, step 3 (b).

x-variable value in case 1	Coefficient			Result
General coefficient	-1.630			-1.630
1 diagnosis (AI)	-1.337	.	1	-1.337
(1 diagnosis (AI))^2	0.413	.	1^2	+0.413
1 diagnosis (AI), group I	0.369	.	1	+0.369
Inability to work 2.0 years	0.0353	.	20	+0.706
Inability to work 2.0 years	-0.0298	.	20	-0.596
Heart volume 1000 ml/m^2	0.000833	.	1000	+0.833
Na^+ in serum 135 mEq/l	0.0178	.	135	+2.403
Na^+ in serum 135 mEq/l	-0.00737	.	135	-0.995
Prime: blood only	-0.201	.	1	-0.201
(Work-load test)^2:22,500	$-2.11.10^{-7}$	.	22,500	-0.005
Acquired lesion 2	0.533	.	2	+1.066
(End-diast. LV)^2:900	0.000193	.	900	+0.174
(Insuff. ao.): degree 4	-0.0408	.	16	-0.653
				+0.547

The predicted death risk is +0.547 or 55 %.

Table 11 refers to text on p. 43.

Table 12. Forecast index built on 31 final regressors, listed in Table 9.

Variable	Limits	Patient belongs to operation group no. I	II+IV	III	V	VI	VII
Heart volume ml/m^2	300	+4	+3	+10	0	-3	+10
	350	6	4	14	0	-4	14
	400	8	5	18	+1	-5	18
	450	10	6	23	1	-7	23
	500	12	7	28	1	-8	28
	550	15	9	34	1	-10	34
	600	17	11	40	1	-12	40
	650	20	13	47	2	-14	47
	700	24	15	54	2	-16	54
	750	27	17	62	2	-19	62
	800	31	19	71	3	-21	71
	850	35	21	80	3	-24	80
	900	39	24	90	3	-27	90
	950	44	27	100	4	-	100
	1000	48	30	111	4	-	111
	1050	53	33	-	4	-	-
	1100	58	36	-	5	-	-
	1150	64	39	-	5	-	-
	1200	69	43	-	6	-	-
	1250	74	46	-	6	-	-
	1300	79	50	-	7	-	-
	1500	-	67	-	9	-	-
	2000	-	118	-	16	-	-
	2500	-	185	-	25	-	-
HCO_3^- in serum mE/l	15	-35			+27		
	16	-30			23		
	17	-25			19		
	18	-20			16		
	19	-15			12		
	20	-10			8		
	21	-5			4		
	22	0	=I	=I	0	=I	=I
	23	+5			-4		
	24	10			-8		
	25	15			-12		
	26	20			-16		
	27	25			-19		
	28	30			-23		
	29	35			-27		
Inability to work years	0-1	0		0	0	0	
	1-2	+9	=I	-30	+8	+2	
	2-3	+15		-49	+13	+4	
	3-4	+21		-69	+18	+6	
	etc. +6 for each year			etc.-20 for each year	etc.+5 for each year	etc.+2 for each year	

Table 12 (continued)

Variable	Limits	Patient belongs to operation group no. I	II+IV	III	V	VI	VII
Length -weight cm - kg	80- 84	-28					
	85- 89	-16					
	90- 94	-7					
	95- 99	-2					
	100-105	0	=I	=I	=I	=I	=I
	106-110	-2					
	111-115	-7					
	116-120	-16					
	121-125	-28					
Belongs to more than one diag. group	1 diagnosis	0	0	—	0	0	0
	2 diagnosis	+8	+8	0	+8	—	—
	3 diagnosis	+133	—	—	—	—	—
Prime contains R+M	0	0	0	0	0	0	0
	1(yes)	-18	-18	-18	-18	-18	-18

Variable	Limits	Patient belongs to operation group no. I	II+IV	V
Type of lesion	Congenital	0		
	Acquired	+35		
End-diastolic pressure in LV mm Hg	2	0		
	3- 7	+1		
	8-12	3		
	13-17	6		
	18-22	10		
	23-27	16		
	28-32	23		
	33-37	31		
	38-42	40		
Systemic blood flow at rest l/min.		Op.group III		
	3	+73		
	4	97		
	5	122		
	6	146		
	7	170		
	8	194		
Aortic gradient at rest mm Hg	0	0		
	5	+37		
	10	+64		
	15	+81		
	20	+87		
	25	+83		
	30	+69		
	35	+45		
	40	+10		
	45	-35		
	50	-90		
Degree of aortic insufficiency	0	0		
	1	-4		
	2	-16		
	3	-35		
	4	-63		
PCV pressure at rest mm Hg	1		0	
	5		-4	
	10		-15	
	15		-33	
	20		-58	
	25		-91	
	30		-131	
	35		-178	
	40		-232	
"Other ECG changes"	Degree 1			+5
	Degree 2			+20
	Degree 3			+44
Systolic PA pressure at rest mm Hg	10		+4	
	20		14	
	30		31	
	40		56	
	50		87	
	60		125	
	70		171	
	80		223	
	90		282	
	100		348	

Table 12 (continued)

Patient belongs to operation group no.

Variable	Limits	III	V
Cl^- in serum mE/l	80	+26	-41
	85	+19	-31
	90	+13	-21
	95	+6	-10
	100	0	0
	105	-6	+10
	110	-13	+21
	115	-19	+31
	120	-26	+41

Variable	Limits	VII
Inability to work years	0 -0.1	0
	0.2-0.3	+8
	0.4-0.6	+19
	0.7-0.9	+31
	1.0-1.5	+48
	1.6-2.0	+69
	2 -3	+96
	3 -4	+134

Variable	Limits	VI
Preoperative Hb value g %	12	-38
	13	-30
	14	-22
	15	-15
	16	-8
	17	0
	18	+8
	19	15
	20	22
	21	30
	22	38
	23	46
	24	53
	25	60

Variable	Limits	VI
Pulmonary gradient at rest mm Hg	10	+49
	20	43
	30	36
	40	30
	50	24
	60	18
	70	12
	80	6
	90	0
	100	-6
	110	-12
	120	-18
	130	-24
	140	-30
	150	-36
	160	-43
	170	-49

	I	II+IV	III	V	VI	VII
General coefficient	+14	-20	-141	-11	+53	-25

Table 12 refers to text on pp. 36-40, 43, 45 and 51.

Table 13. FORECAST INDEX BUILT ON CHOOSEN REGRESSORS (see p. 44).

Table 13 A. Aortic-valve operations

(Operation group I)		Points
Acquired lesion		+11
No. of diagnosis	1	0
	2	+30
	3	+60
Preoperative heart failure	1	0
	2	-8
	3	-15

	Points
Incapacity for work 0 years	0
1 "	+5
2 "	+10
etc.	
General coefficient for group I = -24 points	

Aortic gradient		Age		Heart volume		Work-load test		End-diastol. LV	
Limits	Points	Limits	Points	Limits	Points	Limits	Points	Limits	Points
0	0	15	+2	300	+4	100	0	0	0
5	+1	20	3	350	6	150	0	5	+1
10	2	25	4	400	8	200	-1	10	3
15	3	30	6	450	10	250	-1	15	6
20	4	35	8	500	12	300	-1	20	10
25	5	40	11	550	14	350	-2	25	16
30	6	45	14	600	17	400	-3	30	23
35	7	50	17	650	20	450	-3	35	31
40	8	55	21	700	23	500	-4	40	41
45	9	60	25	750	27	550	-5	45	52
50	10	65	29	800	31	600	-6	50	64
55	11			850	35	650	-7		
60	12			900	39	700	-8		
65	13			950	43	750	-9		
70	14			1000	48	800	-10		
75	15			1050	53	850	-11		
80	16			1100	58	900	-12		
85	17			1150	63	950	-14		
90	18			1200	69	1000	-16		
95	19					1050	-18		
100	20					1100	-19		
105	21					1150	-21		
110	22					1200	-23		
115	23								
120	24								
125	25								

"Acquired lesion" = only indisputable cases of aortic stenosis are denoted "congenital".

"No. of diagnoses" = examples of "more than one diagnosis" are AI + VSD, MI or coronary sclerosis, while AI + AS or AI + AS + aneurysma aortae ascendens constitutes only one diagnosis (see Table 2). Morbid changes outside the heart are disregarded.

"Incapacity for work" = period on sick list, period in receipt of disablement pension or other periods of incapacity for ordinary work.

"Aortic gradient" = at rest during preoperative catheterization (mm Hg).

"Age" = years. "Heart volume" = ml/m^2 BSA. "End-diastolic LV" = at rest preoperatively (mm Hg).

"Work-load test" = the work load the patient was able to manage for 4 minutes, otherwise the preceding load (kpm/min.).

"Preoperative heart failure": see Table 13 B.

Table 13 B. Mitral-valve operations

(Operation group II + IV)		Points
Preoperative heart failure		1 : 0
		2 : +4
		3 : +9
Time of atrial fibrillation	0 years	: 0
	1 "	: -1
	2 "	: -3
	3 "	: -4
	4 "	: -5
	5 "	: -6
	10 "	:-13

General coefficient for group II + IV : +9

Systemic blood-flow		Heart volume		Work-load test		End-diast. LV		Systolic PA	
Limits	Points	Limits	Points	Limits	Points	Limits	Points	Limits	Points
2,0	-9	300	+2	100	0	0	0	0	0
2,5	-11	350	2	150	0	5	-3	5	0
3,0	-13	400	3	200	0	10	-6	10	+1
3,5	-15	450	4	250	+1	15	-9	15	2
4,0	-17	500	4	300	1	20	-12	20	4
4,5	-19	550	5	350	1	25	-15	25	6
5,0	-21	600	6	400	2	30	-18	30	8
5,5	-23	650	7	450	2	35	-21	35	11
6,0	-25	700	9	500	3	40	-24	40	14
6,5	-27	750	10	550	3	45	-27	45	18
7,0	-29	800	11	600	4	50	-30	50	22
7,5	-31	850	13	650	4			55	27
8,0	-33	900	14	700	5			60	32
		950	16	750	6			65	38
		1000	18	800	7			70	44
		1050	19	850	8			75	50
		1100	21	900	8			80	57
		1150	23	950	9			85	64
		1200	25	1000	10			90	72
		1500	40					95	80
		2000	70					100	89
		2500	110						

"Preoperative heart failure": 1 = no preoperative medication
2 = preoperative medication with digitalis
3 = preoperative medication with digitalis + diuretics (more than 2 weeks).

"Time of atrial fibrillation" = duration of irrevercible fibrillation.

"Systemic blood flow" = litres/minute at rest (preoperative catheterization).

"Systolic PA" = systolic pressure in pulmonary artery at rest (mm Hg).

For other definitions, see Table 13 A.

Table 13 C. Combined aortic- and mitral-valve operations

(Operation group III)

	Points
Degree of mitral insufficiency	0 : 0 1 : +10 2 : +20 3 : +30 4 : +40
General coefficient for group III	-60

Aortic gradient		Systemic blood-flow		Heart volume		Work-load test	
Limits	Points	Limits	Points	Limits	Points	Limits	Points
0	0	2,0	+7	300	+5	100	0
5	+8	2,5	10	350	7	150	-1
10	15	3,0	15	400	9	200	-2
15	23	3,5	20	450	11	250	-3
20	30	4,0	27	500	14	300	-4
25	38	4,5	34	550	17	350	-5
30	45	5,0	42	600	20	400	-7
35	53	5,5	50	650	23	450	-9
40	60	6,0	60	700	27	500	-11
45	68	6,5	70	750	31	550	-14
50	76	7,0	81	800	35	600	-16
55	83	7,5	93	850	39	650	-19
60	91	8,0	106	900	44	700	-22
65	98	8,5	120	950	49	750	-26
70	106	9,0	134	1000	54	800	-29
75	113	9,5	150			850	-33
		10,0	166			900	-37
						950	-41
						1000	-46

"Degree of mitral insufficiency": see definition on p. 19, Ch. III.

For other definitions, see Tables 13 A and B.

Table 13 D. Shunt cases except Fallot's tetralogy

(Operation group V)

	Points
"Other ECG changes"	1 : +5 2 : +20 3 : +45
General coefficient for group V	+1

Shunt l/min		PCV at rest		Heart volume		Work-load test	
Limits	Points	Limits	Points	Limits	Points	Limits	Points
0	0	0	0	300	-2	100	0
1,0	+1	5	+4	350	-2	150	-1
2,0	2	10	9	400	-3	200	-2
3,0	3	15	13	450	-3	250	-3
4,0	4	20	17	500	-4	300	-4
5,0	5	25	22	550	-5	350	-6
6,0	6	30	26	600	-6	400	-7
7,0	7	35	30	650	-7	450	-9
8,0	8	40	35	700	-8	500	-11
9,0	9	45	39	750	-10	550	-14
10,0	10	50	43	800	-11	600	-16
11,0	11			850	-12	650	-19
12,0	12			900	-14	700	-22
13,0	13			950	-16	750	-26
14,0	14			1000	-17	800	-29
15,0	15			1050	-19	850	-33
16,0	16			1100	-21	900	-37
17,0	17			1150	-23	950	-41
18,0	18			1200	-25	1000	-46
19,0	19			1500	-39		
20,0	20			2000	-69		

"Other ECG changes" (for definition, see Table 5): 1 = no changes
2 = moderate changes
3 = pronounced changes

"Shunt" (l/min) = the calculated difference between the pulmonary and the systemic blood flow at rest (mm=50).

"PCV" (at rest) = mm Hg.

For other definitions, see Table 13 A.

Table 13 E. Fallot´s Tetralogy

(Operation group VI)

Hypertrophy RV on ECG	1 : 0
	2 : -17
	3 : -34

General coefficient for group VI -114

Gradient RV-PA		O_2 in aorta		Heart volume		Work-load test		Hb value	
Limits	Points	Limits	Points	Limits	Points	Limits	Points	Limits	Points
0	0	50	+32	300	+2	100	0	10	+69
10	-3	55	36	350	3	150	-1	11	76
15	-5	60	39	400	3	200	-2	12	83
20	-7	65	42	450	4	250	-3	13	90
25	-8	70	45	500	5	300	-4	14	97
30	-10	75	49	550	6	350	-6	15	104
35	-11	80	52	600	8	400	-8	16	111
40	-13	85	55	650	9	450	-10	17	118
45	-15	90	58	700	10	500	-12	18	125
55	-18			750	12	550	-14	19	131
60	-20			800	13	600	-17	20	138
65	-21			850	15	650	-20	21	145
70	-23			900	17	700	-23	22	152
75	-25			950	19	750	-27	23	159
80	-26			1000	21	800	-30	24	166
85	-28					850	-34	25	173
90	-30					900	-38	26	180
95	-31					950	-42	27	187
100	-33					1000	-47	28	194
105	-34							29	201
110	-36							30	208
115	-38								
120	-39								

"Hypertrophy RV on ECG": 1 = no hypertrophy

2 = moderate hypertrophy

3 = pronounced hypertrophy of right ventricle

"Gradient RV-PA" = the systolic gradient over the pulmonary ostium measured at rest pre-operatively (mm Hg).

"O_2 in aorta" = oxygen saturation at rest.

"Hb value" = g %.

Table 13 refers to text on pp. 44-46, 51-52.

Table 14. Coefficient values for 29 regressors. In column R original coefficient values and in column M the corresponding values after correction of the irregular errors in some of the regressors. y = 30-day postoperative mortality. Undeleted regressors from step 2 in final analysis.

Regressors	Col R	Col M
Length minus weight	0.145	0.337
More than one diagnosis	-0.343	-0.743
Incapacity for work	0.0353	-0.0551
HCO_3^- value in serum	0.0464	0.0852
Prime contains R + M	-0.197	-0.0528
Op. group III x Systemic blood-flow	0.0195	0.102
Op. group III x Aortic gradient	0.0114	0.0174
(Length minus weight)^2	-0.000709	-0.00168
(More than one diagnosis)^2	0.171	0.318
(Heart volume)^2	1.03×10^{-6}	6.82×10^{-6}
Op. group I x (End-diastolic pressure LV)^2	0.000249	0.000519
Op. group I x (Degree of aortic insufficiency)^2	-0.0376	-0.0366
Op. group II + IV x (PCV)^2	0.000346	0.00169
Op. group I x Congenital or acquired lesion	0.295	0.750
Op. group I x Incapacity for work	-0.0293	0.0576
Op. group I x (Heart volume)^2	-5.76×10^{-7}	-7.05×10^{-6}
Op. group II + IV x Incapacity for work	-0.0336	0.0708
Op. group II + IV x (heart volume)^2	-8.53×10^{-7}	-6.71×10^{-6}
Op. group III x Incapacity for work	-0.0561	0.0666
Op. group III x Cl^- in serum	-0.0108	-0.0888
Op. group V x Incapacity for work	-0.0348	0.0561
Op. group V x Cl^- in serum	0.0197	0.0350
Op. group V x HCO_3^- in serum	-0.0898	-0.142
Op. group V x (Heart volume)^2	-9.85×10^{-7}	-6.71×10^{-6}
Op. group V x ("Other ECG changes")^2	0.0512	0.0760
Op. group VI x Incapacity for work	-0.0339	0.0545
Op. group VI x Pulmonary gradient	-0.00662	-0.0230
Op. group VI x (Heart volume)^2	-1.44×10^{-6}	-6.47×10^{-6}
Op. group VI x Preoperative Hb value	0.0758	0.205

Note. "More than one diagnosis" means that the patient belongs to more than one of the "diagnostic groups" (see Table 2).

Table 14 refers to text on pp 49-50

Table 15. Regression coefficients of 20 undeleted regressors in analysis of pre- and peroperative factors. The figures in brackets are the coefficient values for preoperative factors after analysis of the patient's preoperative states only. All regressors have t-ratios > 3.36. y = mortality within 30 days.

Regressors	Regression coefficient	
Patient belongs to more than 1 diagnostic group	-2.444	(-1.790)
(Patient belongs to more than 1 diagnostic group)^2	0.833	(0.617)
Inability to work (years)	0.537	(0.602)
(Heart volume)^2 (ml/m^2)	1.24×10^{-6}	(1.38×10^{-6})
Op. group I x congen. or acq.lesion	0.603	(0.470)
Op. group I x inability to work	-0.0464	(-0.0541)
Op. group I x (degree of aortic insufficiency)^2	-0.0358	(-0.0411)
Op. group II + IV x inability to work	-0.0566	(-0.0623)
Op. group II + IV x (heart volume)^2	-1.05×10^{-6}	(-1.20×10^{-6})
Op. group III x inability to work	-0.0727	(-0.0478)
Op. group V x inability to work	-0.0541	(-0.0601)
Op. group V x Cl^- in serum (mE/l)	0.00651	(0.00520)
Op. group V x (heart volume)^2	-1.28×10^{-6}	(-1.35×10^{-6})
Op. group VI x inability to work	-0.0565	(-0.0597)
Op. group VI x preoperative Hb-value (g%)	0.0751	
Operation time (hours)	0.0718	
Re-operation on account of bleeding	0.532	
Weight difference after op. minus before op. (kg)	-0.0354	
Length of fall in BP < 80 mm Hg during ECC	0.0438	
Administration of K^+ during op. day (mE/kg BW)	-0.106	

Table 15 refers to text on pp 53-56.

Table 16. Number of patients in the three different classifications of postoperative renal function, mean values and SE of non-protein nitrogen (NPN) in serum.

"Renal group"	No of patients	Mean values + SE of NPN (mg % in serum)						
		Preop.	Day 1	2	3	4	5	10
1	92	31±0.5	33±0.5	34±0.6	32±0.6	30±0.6	30±0.5	30±0.6
2	74	33±0.5	42±0.9	50±1.2	54±2.0	52±2.4	51±2.8	43±2.3
3	15	28±0.9	48±2.5	63±4.5	85±10.7	92±11.5	102±12.7	115±15.0

"Renal group" 1 = Postoperative renal function unimpaired.
"Renal group" 2 = Clinical signs of impaired postoperative renal function.
"Renal group" 3 = Postoperative acute renal failure.

Table 16 refers to text on pp.60-61.

Table 17. Mean values ± SE of urine volume, creatinine clearance and the urine/blood ratios of urea and creatinine in three different renal classifications.

Variable	"Renal group"	Mean values and SE during different intervals: Before ECC	During ECC	After ECC	During rest of op. day	Day 1	Day 2	No. of patients
Urine volume	1	1.12±0.16	2.10±0.33	2.79±0.22	0.79±0.03	0.64±0.03	0.72±0.03	77
(ml/kg/hour)	2	0.64±0.10	2.11±0.33	2.21±0.20	0.71±0.04	0.68±0.04	0.77±0.04	48
	3	0.57±0.14	1.08±0.28	1.47±0.31	0.55±0.10	0.38±0.13	0.30±0.14	10
Creatinine	1	86±13	16± 2	103± 9	78± 4	99± 5	108± 5	65
clearance	2	49± 7	11± 2	61± 6	45± 5	64± 7	70± 7	40
(ml/min)	3	23± 6	5± 1	23± 7	14± 5	4± 1	2± 1	10
Urine/blood	1	30± 2	13± 2	14± 2	33± 3	47± 3	59± 4	63
urea ratio	2	26± 3	10± 2	7± 1	13± 2	16± 2	23± 3	36
	3	29± 6	10± 3	7± 1	6± 2	3± 1	3± 1	10
Urine/blood	1	103± 9	70±13	41± 4	106± 7	155± 7	156± 8	65
creatinine	2	84± 9	55±10	31± 4	59± 6	88± 9	81± 7	40
ratio	3	44±10	29± 7	20± 5	24± 6	9± 2	5± 1	10

Table 17 refers to text on p. 61.

Table 18. Undeleted regressors after analysis of pre- and peroperative factors at p-level 0.95. y = postoperative renal function.

Regressors	Regression coefficients and significance levels
2 Congenital- acquired lesion	$0.535^{(+++)}$
25 Preoperative creatinine clearence (ml/min)	$-0.00461^{(++)}$
10 $(\text{Heart volume})^2$ (ml/m^2)	$3.28 \cdot 10^{-7(+++)}$
26 Prime containes blood	$-0.248^{(+)}$
3 Operation group II + IV	$-0.478^{(++)}$
6 Operation group I x $(\text{aortic insufficiency})^2$	$-0.092^{(++)}$
12 Operation group I x $(\text{end-diastolic pressure in LV (mm Hg)})^2$	$0.000293^{(+)}$
16 Operation group III x $(\text{heart volume})^2$	$4.35 \cdot 10^{-6(++)}$
30 Total perfusion time (minutes)	$0.00477^{(+++)}$
32 Lowest esophageal temperature during total perfusion (deg. C)	$-0.00550^{(+++)}$
34 Reoperation on account of postoperative bleeding	$0.553^{(++)}$
37 Complications during operation	$0.339^{(+++)}$
39 Urinary volume during op.day (ml/kg/ h)	$-0.0170^{(+++)}$
40 Weight difference during op (after minus before)	$-0.0193^{(+)}$
41 Length of blood pressure falls <80 mm Hg during ECC	$0.0450^{(+)}$
45 Length of perfusion of right coronary artery x Op. group III	$-0.0139^{(+)}$
47 No of Starr ball-valve in aorta x op. grp III	$-0.199^{(++)}$
52 Fibrinogen given during op-day (g/kg)	$-9.88^{(+)}$
60 White bloodcell count during ECC	$0.00297^{(+)}$
65 Arterial blood pH during op. before ECC	$0.0996^{(+)}$
66 Arterial blood pH during ECC	$-0.0901^{(+)}$
73 Arterial blood pCO_2 during op. before ECC	$0.00749^{(+)}$
74 Arterial blood pCO_2 during ECC	$-0.00830^{(++)}$
77 Arterial blood HCO_3^- -value during op. before ECC	$-0.0183^{(+)}$
78 Arterial blood HCO_3^- -value during ECC	$0.0192^{(+)}$
80 Arterial blood HCO_3^- -value during op. after ECC	$-0.00567^{(++)}$

Table 18 refers to text on p. 63.

Table 19. xx and xy correlations between 14 undeleted regressors with at least(**) significance in the final analysis (step 5) of the pre- and peroperative factors. The numbers of the x-variables correspond to those in Table 18. y = postoperative renal function. ø = coefficient value between ±0.10.

2	3	6	10	16	25	30	32	34	37	39	47	74	80	x	y
	.25***	.48***	.21**	.16*	-ø	.28***	.20**	-ø	-ø	-.20**	.16*	.12	.15*	2	.26***
		-.35***	.34***	-ø	-ø	-.13	-ø	-ø	-ø	-ø	-ø	-ø	-ø	3	ø
			-ø	-.20**	.25***	.15*	.26***	-ø	-ø	-ø	-.20**	.20**	.11	6	-ø
				ø	-ø	ø	.11	-ø	.12	-ø	ø	-ø	ø	10	.30***
					-.10	.35***	-ø	-ø	ø	ø	.98***	-ø	ø	16	.18*
						-ø	-ø	ø	-ø	-ø	-.11	ø	ø	25	-.20**
							-.21**	ø	.14	-ø	.34***	.14	ø	30	.39***
								-.18*	ø	-ø	-ø	-ø	-ø	32	-.16*
									-ø	-ø	-ø	ø	.11	34	.18*
										-ø	ø	.12	.22**	37	.27***
											ø	-.18*	ø	39	-.30***
												-ø	ø	47	.17*
													ø	74	ø
														80	-ø

Table 19 refers to text on pp. 63–64.
For definition of regressors, see Table 18.

Table 20. Distribution of patients with different primes in postoperative-renal-function classifications.

Prime	No. of patients in renal classification 1	2	3	Total
B	18	19	1	38
B + R	22	20	8	50
B + M	14	15	1	30
B + Gl	8	8	3	19
B + R + M	19	3	1	23
R + M	11	9	0	20
M	0	0	1	1

B	denotes prime with blood only
B + R	denotes prime with blood + Rheomacrodex
B + M	denotes prime with blood + mannitol
B + Gl	denotes prime with blood + 5.5 % glucose
B + R + M	denotes prime with blood + Rheomacrodex + mannitol
R + M	denotes prime with Rheomacrodex + mannitol, without blood
M	denotes prime with mannitol (+ other fluids than Rheomacrodex), without blood.

Table 20 refers to text on p. 68.

Table 21. Means ± SD of observed values in remaining peroperative regressors with at least (*) significance after final analysis of postoperative renal function.

Regressors	Observed value	
	Mean	SD
Perfusion time (min.)	79.0 ±	33.5
Lowest esophageal temp. (^{o}C)	32.2 ±	7.3
Urinary volume during op.day (ml/kg)	22.1 ±	10.3
pCO_2 during ECC (mm Hg)	34.3 ±	4.2
HCO_3^- 0-3 hours after ECC (mE/l)	22.1 ±	2.0
Duration of falls in BP < 80 mm Hg (min.)	16.6 ±	3.3
pH during ECC	7.43±	0.06

Table 21 shows the distribution of some peroperative variables in the present material, thus giving an idea of the base on which the regression coefficients were calculated. The mean values and range of the individual regressors are of interest only in comparisons with other materials (see text on p. 73).

APPENDIX II

ABBREVIATIONS AND UNITS

For statistical symbols, see Ch. III, B.

ECG symbols according to international usage.

Most of the other symbols or abbreviations listed in this appendix are also explained in the text, when first used, and in the tables.

A. AC = alternating current (shock)
ACD = acid-citrate-dextrose (blood)
Acq. = acquired (heart lesion)
AI = Ao. insuff. = insufficiency in aortic valves (pp. 18-19)
Aorta or aortic lesion = aortic-valve lesion
Aneur. ao. = aortic aneurysm
AS = aortic-valve stenosis
ASD sec., ASD prim. = ostium-secundum or ostium-primum defects
AV com. = common atrio-ventricular canal
AV block = atrio-ventricular block

B. B = prime contains blood
B only = prime contains only blood
BP = systolic blood pressure (mm Hg)
BSA = body-surface area (m^2)
Bubble = bubble oxygenator
BUN = blood urea nitrogen (mg %)
b.w. or BW = body weight (kg)

C. CDC = Control Data Corporation
Coeff. = coefficient
Cl^- = chloride ion concentration (mE/l)
cong., congen. = congenital (heart lesion)
Com. tomy = commissurotomy

D. D.C. = direct current (shock)
Diagn., diagnostic, diagnosis group (see p. 17, Table 2)
Diast. = diastolic blood pressure (mm Hg)
Dil. = dilatation
Disc = disc oxygenator
D/W = dextrose in water

E. ECC = extra-corporeal circulation
ECG = electrocardiogram (see p. 19)
End-diast. = end-diastolic pressure (mm Hg)
ES = extra systoles

G. GFR = glomerular filtration rate
Gl = glucose

H. h = hour
Hb = hemoglobin (g %)
HCO_3^- = bicarbonate ion concentration (mE/l)

I. I = insuff. = insufficiency
IS = infundibular stricture
IU = international unit

K. K^+ = potassium ion concentration (mE/l)

L. LV = left ventricle

M. M = prime contains mannitol
mE = milliequivalent
M_w = mean molecular weight
MI = mitral insufficiency (p. 19)
"Mortality group": definition on p. 29 and in Table 6 A
MS = mitral stenosis

N. Na^+ = sodium ion concentration (mE/l)
NPN = non-protein nitrogen (mg %)

O. O_2 = oxygen (saturation)
obs. = (time of) observation
Op. group = "operation group" (Table 3)
"Other ECG changes" = definition in Table 5 and on p. 20

P. PA = pulmonary artery
PAH = para-amino-hippurate
PCV = pulmonary capillary vein (pressure; mm Hg)
pCO_2 = partial pressure of carbon dioxide (mm Hg)
pO_2 = partial pressure of oxygen (mm Hg)
preop. preoperative
PS = pulmonary stenosis
pulm. = pulmonary

R. r, R, R^2 as statistical symbols, see p. 24 and Table 8
R = prime contains Rheomacrodex
® = denotes proprietary names of drugs
"Renal group" = for definition, see p. 59
Res. = resection
RPF = renal plasma flow
RV = right ventricle

S. Starr = Starr-Edwards ball-valve prosthesis
Sub AS = sub-aortic stenosis
Syst BP = systolic blood-pressure

T. Tham, Tris = tris-hydroxy-methyl-amino-methane
TI = tricuspidal insufficiency

V. Valv. = valve(s) or valvular
VES = ventricular extra systoles
VSD = ventricular septal defect

W. WRAP = weighted regression-analysis program (pp. 26, 31)

APPENDIX III

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